

**Research Article****PREVALENCE OF HEART DISEASE IN PREGNANCY; JANUARY 2021 TO JANUARY 2022 AT BENGHAZI MEDICAL CENTER****<sup>1,\*</sup> Intesar Elmejresy, <sup>2</sup>Nagat Bettamer, <sup>1</sup>Salwa Benkia and <sup>2</sup>Nagat Omar Maadani**<sup>1</sup>Consultant of Obstetrics and Gynecology in Benghazi Medical Center and member of the teaching staff at Faculty of Medicine, University of Benghazi, Libya<sup>2</sup>Consultant of Obstetrics & gynecology in Aljamhoria hospital and member of the teaching staff at Faculty of Medicine, University of Benghazi, Libya**Received 12<sup>th</sup> November 2023; Accepted 18<sup>th</sup> December 2023; Published online 30<sup>th</sup> January 2024**

---

**Abstract**

Cardiovascular disease has been estimated to be present in 0.1 -4% of pregnancies. <sup>(1)</sup> The incidence of pregnancies in women with heart disease is rising, mainly due to an increased number of women with congenital heart disease (CHD) Reaching childbearing age, advancing maternal age, and increased incidence of risk factors including; diabetes mellitus, hypertension, preeclampsia, and multifetal pregnancies. Although the majority of women with cardiac disease can become pregnant and, with early diagnosis and appropriate management, can be brought to term safely, they are high risk cardiac conditions that may be associated with important morbidity and even mortality. <sup>(2)</sup> Although pregnancies complicated by heart disease are rare in the UK, Europe and developed world, cardiac disease is now the leading cause of maternal death in the UK (CEMACH). <sup>(3)</sup> GIVING a death rate of 2.2 per 100,000 maternities. The maternal mortality rate from cardiac disease has continued to rise since 1980, the major causes of cardiac death are cardiomyopathy, myocardial infarction (coronary artery disease), dissection of aorta, and pulmonary hypertension .in the UK rheumatic heart disease is extremely rare in women of childbearing age and mostly confined to immigrants. They have been no maternal deaths reported from rheumatic heart disease since 1994, so heart diseases during pregnancy are the leading indirect cause of maternal death worldwide <sup>(4)</sup>.

**Keywords:** Heart Disease, Pregnancy.**INTRODUCTION**

Cardiovascular disease has been estimated to be present in 0.1 -4% of pregnancies. <sup>(1)</sup> The incidence of pregnancies in women with heart disease is rising, mainly due to an increased number of women with congenital heart disease (CHD) Reaching childbearing age, advancing maternal age, and increased incidence of risk factors including; diabetes mellitus, hypertension, preeclampsia, and multifetal pregnancies. Although the majority of women with cardiac disease can become pregnant and, with early diagnosis and appropriate management, can be brought to term safely, they are high risk cardiac conditions that may be associated with important morbidity and even mortality. <sup>(2)</sup> Although pregnancies complicated by heart disease are rare in the UK, Europe and developed world, cardiac disease is now the leading cause of maternal death in the UK (CEMACH). <sup>(3)</sup> GIVING a death rate of 2.2 per 100,000 maternities. The maternal mortality rate from cardiac disease has continued to rise since 1980, the major causes of cardiac death are cardiomyopathy, myocardial infarction (coronary artery disease), dissection of aorta, and pulmonary hypertension .in the UK rheumatic heart disease is extremely rare in women of childbearing age and mostly confined to immigrants. They have been no maternal deaths reported from rheumatic heart disease since 1994, so heart diseases during pregnancy are the leading indirect cause of maternal death worldwide <sup>(4)</sup>

**Physiological cardiovascular changes**

Blood volume increases substantially during pregnancy, starting as early as the six weeks and rising until mid-pregnancy, when the rise continues at a slower rate, with an average maximum increase of 50%. <sup>(5,6)</sup> Because the red blood cell mass increase less rapidly, the hemoglobin concentration falls, causing the physiological anemia of pregnancy. Cardiac output during pregnancy increases by about 50%, predominantly due to augmentation of stroke volume during early pregnancy and increased heart rate in the third trimester. Systemic blood pressure falls during the first trimester, reaching more fall in 2nd trimester and returning toward pre-pregnancy levels before term. This change results from a decline in systemic vascular resistance due to reduced vascular tone. Hemodynamics are altered substantially during labor and delivery, secondary to anxiety, pain, and uterine contractions, oxygen consumption increases 3-folds and systolic and diastolic Bp rise during contraction. <sup>(7)</sup> Immediately. Following delivery, relief of vena caval compression and auto transfusion from the emptied and contracted uterus produce a further increase in cardiac output. Physiological changes in the cardiovascular system during pregnancy may bear a risk for those with heart disease who are not able to sufficiently adapt and can be complicated by myocardial infarction, cardiomyopathies, arrhythmias, thromboembolic disease, cerebrovascular disease, and heart failure. Although there is a significant risk involved with such pregnancies, one can successfully treat the majority of these incidents if early detection and careful follow up are a part of routine care.

---

**\*Corresponding Author: Intesar Elmejresy,**

Consultant of Obstetrics and Gynecology in Benghazi Medical Center and member of the teaching staff at Faculty of Medicine, University of Benghazi, Libya

## LITERATURE REVIEW

The frequency of cardiac disease in women has not been clearly established. It is also unknown if there is an increased frequency of individuals in developed vs. under-developed countries. Based on the best data, estimates are that at least 0.2% of pregnancies have complications with cardiac disease.<sup>(8)</sup> This frequency has been reported to be as high as 4%. If one includes hypertensive disease in this value, this number would be even higher, given that hypertensive disorders have been approximated to occur in up to 8% of pregnancies.<sup>(9)</sup> At the National Maternity Hospital, Dublin, Ireland, during the years 1969 to 1978, were reviewed. The incidence was 0.5%. Three hundred twenty-three (83.5%) were of rheumatic origin, 52 (13.4%) were congenital, and the remaining 12 (3.1%) were a miscellaneous group and included cases of cor-pulmonale and coronary artery disease. There were two maternal deaths--one from congenital heart disease and one from postpartum suicide, unrelated to mild rheumatic heart disease. The perinatal mortality rate was 3.3%. Five pregnancies (three patients) were complicated by surgically uncorrected cyanotic congenital heart disease. One of the maternal deaths and three of the perinatal deaths occurred in this group. There were 38 episodes of cardiac failure (38 patients) in cases of rheumatic heart disease. The New York Heart Association grading was grade 1 in 15 (39%) of these before the onset of failure. Prophylactic antibiotics were not used and infective endocarditis did not occur. Therapeutic abortion was not practiced and a conservative approach was adopted in obstetric.<sup>(10)</sup> Between 1970 and 1983, 519 pregnancies in 405 women with heart disease were managed at the Royal Maternity Hospital, Belfast, Northern Ireland, a rate of 1.3 per 100 deliveries. In 312 (60%) the heart disease was of rheumatic origin, in 161 (31%) congenital, and the remaining 46 (9%) were a miscellaneous group that included arrhythmias, ischemic heart disease and cardiomyopathies. The New York Heart Association (NYHA) grading was no greater than 1-2 in 445 (86%) pregnancies antenatally. Three maternal deaths occurred, all in the group whose antenatal NYHA grade was 3-4. Heart failure was present in 96 (18%) pregnancies antenatally, and six others developed failure during labour or in the puerperium. Prophylactic antibiotics were not used routinely and infective endocarditis did not occur. The perinatal mortality rate was 19/1000, and the rate of congenital malformations was not raised in the reviewed group.<sup>(11)</sup>

Cardiovascular disease (CVD) is the leading cause of pregnancy-related mortality in the United States and has gradually increased over time (from 7.2 to 17.2 deaths per 100 000 live births from 1987–2015). The rise in maternal mortality has been attributed to increasing numbers of women at advanced maternal age undertaking pregnancy, comorbid preexisting conditions such as diabetes mellitus and hypertension, and the growing number of women with congenital heart disease surviving to childbearing age. Racial and ethnic disparities in pregnancy-related mortality are significant, peaking among black non-Hispanic women followed by American Indian/Alaskan Native non-Hispanic women, Asian/Pacific Islander non-Hispanic women, white non-Hispanic women, and Hispanic women (42.8, 32.5, 14.2, 13.0, and 11.4 deaths per 100 000 live births, respectively).<sup>(12)</sup> In the UK, the Confidential Enquiries into Maternal Deaths (CEMACH) have shown that the overall rate of mortality from cardiac disease has risen from 7.3/million births in the 1982–84 triennium1 to 22.7/million births in the 2003–05

triennium.2 The major part of this increase is attributable to acquired heart disease, deaths from which have risen from 4.7/million births to 20.8/million births. One-third of these deaths are a result of myocardial infarction/ischemic heart disease and a similar number of late deaths are associated with peripartum cardiomyopathy. Other significant contributors (5–10% each) are rheumatic heart disease, congenital heart disease and pulmonary hypertension. With the current increase in older mothers, obesity, immigration and survival of babies operated on for congenital heart disease, the need to identify women at risk of heart disease and to plan their careful management will also inevitably increase. The suggestions in this Good Practice guidance are based upon the recommendations of a consensus group convened at the Royal College of Obstetricians and Gynecologists in 2006, which are published in full by the RCOG Press, 3 and those in the CEMACH report Saving Mothers' Lives: Reviewing Maternal Deaths to Make Motherhood Safer 2003–2005.<sup>(13)</sup> Pregnancy itself raises the risk of acute myocardial infarction by three- to four-fold, with the risk being 30 times higher for women over the age of 40 years compared with women aged less than 20 years. As reported by CEMACH, in the 2003–05 triennium2 the rate of maternal death from ischemic heart disease in the UK had risen to 1/132,000 pregnancies (up from 1/252,000 in 2000–2002).<sup>(14)</sup>

In total, 1,938 pregnancies were included. Cardiac complications occurred in 16% of pregnancies and were primarily related to arrhythmias and heart failure. Although the overall rates of cardiac complications during pregnancy did not change over the years, the frequency of pulmonary edema decreased (8% from 1994 to 2001 vs. 4% from 2001 to 2014; *p* value = 0.012). Ten predictors of maternal cardiac complications were identified: 5 general predictors (prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk valve disease/left ventricular outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions); 4 lesion specific predictors (mechanical valves, high-risk aortopathies, pulmonary hypertension, coronary artery disease); and 1 delivery of care predictor (late pregnancy assessment). These 10 predictors were incorporated into a new risk index (CARPREG II [Cardiac Disease in Pregnancy Study]). Pregnancy in women with heart disease continues to be associated with significant morbidity, although mortality is rare. Prediction of maternal cardiac complications in women with heart disease is enhanced by integration of general, lesion-specific, and delivery of care variables.<sup>(15)</sup> Reducing maternal mortality is a World Health Organization (WHO) global health goal. Although maternal deaths due to hemorrhage and infection are declining, those related to heart disease are increasing and are now the most important cause in western countries. The aim is to define contemporary diagnosis-specific outcomes in pregnant women with heart disease.

From 2007 to 2018, pregnant women with heart disease were prospectively enrolled in the Registry of Pregnancy and Cardiac disease (ROPAC). Primary outcome was maternal mortality or heart failure, secondary outcomes were other cardiac, obstetric, and fetal complications. We enrolled 5739 pregnancies; the mean age was 29.5. Prevalent diagnoses were congenital (57%) and valvular heart disease (29%). Mortality (overall 0.6%) was highest in the pulmonary arterial hypertension (PAH) group (9%). Heart failure occurred in 11%, arrhythmias in 2%. Delivery was by Caesarean section in

44%. Obstetric and fetal complications occurred in 17% and 21%, respectively. The number of high-risk pregnancies (mWHO Class IV) increased from 0.7% in 2007-2010 to 10.9% in 2015-2018. Determinants for maternal complications were pre-pregnancy heart failure or New York Heart Association >II, systemic ejection fraction <40%, mWHO Class 4, and anticoagulants use. After an increase from 2007 to 2009, complication rates fell from 13.2% in 2010 to 9.3% in 2017.<sup>(16)</sup> Rates of maternal mortality or heart failure were high in women with heart disease. However, from 2010, these rates declined despite the inclusion of more high-risk pregnancies. Highest complication rates occurred in women with PAH. The association between heart disease and pregnancy is increasingly prevalent. Although most women with heart disease tolerate the physiological changes of pregnancy. Some of these diseases may be exacerbations of pre-existing conditions that the pregnant woman may already have, or they may develop a new disease process that presents because of the complex hormonal changes and physiology of pregnancy. Pre-existing conditions which can predispose the pregnant woman to cardiovascular disease include hypertension, diabetes mellitus, and congenital heart disease.<sup>(17)</sup> Regardless, cardiac disease of pregnancy is a significant cause of or morbidity and mortality and has been present between 1-4% of all pregnancies. Although there is a significant risk involved with such pregnancies, one can successfully treat the majority of these incidents if early detection and careful follow-up are a part of routine care.

#### Normal finding in CVS during pregnancy

- Pulse rate increases.
- Diastolic BP decreases.
- first heart sound is prominent and split.
- Second heart sound normal.
- Third heart sound normally not heard but in pregnancy it is prominent.
- Ejection systolic murmur heard normally in aortic or pulmonary area at 10-12 weeks due to expanded intravenous volume heard in 90% cases.
- A soft diastolic murmur is heard in 10% cases.
- Continuous murmur heard normally over the tricuspid area in left 2-3rd intercostal space heard in 10% cases.
- Apex beat is heard in fourth ICS, 2.5 cm left to midclavicular line.
- Slight cardio exalts on X-ray.
- EGG left axis deviation<sup>(18)</sup>.

#### Physiological change in pregnancy

Pregnancy is associated with various physiological adaptations of the cardiovascular system.<sup>(19,20,21)</sup> Cardiac output needs to increase up to 50% during pregnancy, to enable the fetal circulation, and this increase starts already during the first trimester. There is a 30%–40% decrease in vascular resistance. As part of the cardiac output, plasma volume expands in the first and second trimester, followed by an increase in heart rate of around 10%–20%. Delivery further pushes these changes to a temporary maximum. After delivery, large fluid shifts are responsible for a transient volume overload in the first day's post-partum. As a consequence of these hemodynamic changes, echocardiographic studies show a clear increase in left ventricular end-diastolic dimensions, while the systolic measurement remain stable.<sup>(22)</sup> The subsequent increase in

stroke volume leads to a rise of the ventricular outflow tract velocity, and it mimics a hyperkinetic state. The same probably holds for the right ventricle, although less evidence is available. Finally, the expansion of stroke volume and lower afterload influence absolute regurgitation volumes. Regurgitated lesions will therefore hardly be worse during pregnancy. Hormonal changes influence the integrity of the vessel wall. The structure of the aortic wall may have a weaker composition, which is not of significant importance to healthy women, but may enhance the risk of aortic dissection in women with aortic disease. Furthermore, pregnancy is known for its hypercoagulable state, which is very relevant in those with a mechanical prosthetic heart valve or Fontan circulation. Pharmacokinetic processes will change during pregnancy, due to the increased plasma volume and total body water, and through changes in absorption, glomerular filtration rate, hepatic metabolism and protein binding activity. Moreover,<sup>(23)</sup> drugs may cross the placental border and reach the fetal circulation. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) provide available evidence for medication during pregnancy, which is helpful when considering or revising drug therapy during pregnancy and breast feeding. Medication used before pregnancy should be evaluated for teratogenicity. ACE inhibitors and angiotensin receptor blockers (ARB) have potential adverse effects on the fetus and are therefore contraindicated. In women who are prescribed ACE inhibitors or ARB, a pre pregnancy trial without these agents may show whether they remain stable. In women with high risk of heart failure, already pregnant, the risk of discontinuing may outweigh potential fetal risks, a balance to be made by the physician. Beta-blockers can be continued, with strict fetal monitoring because of potential low birth weight. Atenolol is contraindicated during pregnancy, because of reported birth defects. Life-threatening acute heart failure during pregnancy should be treated as outside pregnancy, with no restrictions, to enable the mother to survive such a hazardous event. The FDA classification has been replaced by the Pregnancy and Lactation Labelling Rule, and can be found in prescription labels, and online on the website of both the FDA<sup>42</sup> and the EMA.<sup>43</sup> Evaluation of this information is key to enable counselling and provide the best available information on medication during pregnancy

#### Cardiac output: Estimates for increases

In a cardiac output range from 20 to 50%. These findings are seen within the first 5 weeks of gestation and increase until the late gestational age; this is usually accounted for by an increased stroke volume of about 25% in the first trimester. This considerable increase in the cardiac output is one reason why pregnant women with pre-existing heart conditions can experience such dramatic effects, especially later on in pregnancy. Those with diseases such as cardiomyopathy may not adequately compensate for this stress and may develop complications such as pulmonary edema or fluid overloaded states.<sup>(24)</sup>

- **Heart rate:** Along with an increase in stroke volume, there is an increase in heart rate of approximately 15 to 30% in the first trimester of pregnancy, which also contributes to an increase in cardiac output.
- **Systemic vascular resistance:** Systemic vascular resistance decreases during pregnancy. Estimates are that this change may be as much as 30%. Some hormonal changes include decreased responsiveness of maternal

vasculature to angiotensin II and norepinephrine.<sup>(25)</sup> There is also an increased rate of release of vasodilators in the maternal female such as prostaglandins and nitric oxide.<sup>(26)</sup>

- **Blood pressure:** Blood pressure slightly decreases early in pregnancy. Overall, more commonly diastolic blood pressure decreases predominate over-systolic blood pressure early in pregnancy. Usually, this value normalizes, or even increases by the end of pregnancy

### Hemodynamic adaptations to pregnancy

Important adaptations to the cardiovascular system occur in response to pregnancy to meet the increasing metabolic needs of both mother and fetus non-adaptive hemodynamic previously unknown disease, and hence pregnancy is often considered a natural stress test.<sup>(27)</sup> Blood volume increases considerably during pregnancy, rapidly between six and 20 weeks, and less markedly between 20 weeks and term, with a mean overall increase of around 50%.<sup>(28)</sup> Increased erythropoietin production stimulates erythropoiesis, which can rise by over 40% in a pregnant woman without nutritional deficiencies.<sup>(29)</sup> However, the increase in plasma volume is greater than that of red blood cell mass, resulting in hemodilution, which leads to physiological anemia of pregnancy. Hemoglobin levels as low as 11 g/dl are considered physiological. Cardiac output (CO) rises by around 50%, initially due mainly to increased systolic volume and then to increased heart rate (HR) in the third trimester. Peripheral vascular resistance (PVR) falls during pregnancy, leading to reductions in systolic and diastolic blood pressure (BP).

BP is lowest during the second trimester (5-10 mmHg below initial levels), although the steepest BP falls occur between six and eight weeks of pregnancy.<sup>(30)</sup> As pregnancy-related changes in BP occur very early, BP levels later in the pregnancy should be compared with those before pregnancy, rather than with those recorded in the first weeks. During the third trimester, BP returns to pre-conception levels. CO reaches a peak in labor and immediately after delivery, with an increase of 60-80%. This is due to various factors, particularly higher HR, increased preload associated with uterine contractions (for each uterine contraction 300-500 ml of blood enters the systemic circulation), and elevation of circulating catecholamine's.<sup>(31)</sup> It is extremely important to maintain blood volume at this stage and care should be taken to avoid excessive blood loss, which could drastically reduce preload. This is the stage at which there is greatest risk of decompensation of heart disease. A combination of the above physiological and hormonal changes are hypothesized as contributing to certain decompensated states of pregnancy such as cardiomyopathy, congenital heart diseases, and valvular disease. It is, however, without doubt, that specific structural changes occur to the maternal heart, and such changes can cause dysfunctional some of these pre-existing diseases. Because of the increase in the volume of pregnancy, a common effect is an enlargement of both atria and both ventricles by the end of pregnancy.<sup>[32]</sup> Left ventricular mass increases by up to 50% by the third trimester and eccentric hypertrophy is also noted with increases in septal thickness.<sup>(33)</sup> Some degree of cardiac remodeling exists to the maternal heart, as many of the changes that occur to the maternal heart are often seen to be reversed 6 to 8 months postpartum.<sup>(34)</sup> For disease processes such as peripartum cardiomyopathy.<sup>(35)</sup> It is easy to see why such dramatic changes would contribute to exacerbation of disease processes. However, no specific studies have

concluded the exact reason these females are much more vulnerable to this disease process than others. Therefore, theories such as concurrent myocarditis, an autoimmune phenomenon, or familial linkage are potential explanations towards resultant peripartum cardiomyopathy.<sup>(30)</sup> In mouse models, mis-regulation of VEGF and angiogenesis have been theorized to have a vital role in this disease process.<sup>(36)</sup> Regarding pre-existing valvar disorders such as mitral stenosis, mitral regurgitation, aortic stenosis, and others, the chamber and valvar enlargement along with a potential volume overloaded state can contribute to morbidity and mortality. All of these conditions can contribute to the fluid overloaded state, and place patients at risk for respiratory compromise, and poorly perfused states.

### PREGNANCY AND HEART DISEASE

Although maternal cardiac disease complicates a small percentage of pregnancies overall, it is a significant cause of non-obstetrical maternal and fetal morbidity and mortality.<sup>(32)</sup> Pregnancy is associated with significant hemodynamic changes, namely volume expansion and increased cardiac output, which in the setting of underlying maternal cardiac disease may lead to decompensation and fetal demise. In addition to the hemodynamic changes imposed by the gravid state, factors such as peripheral vasodilation from anesthesia or blood loss that may occur with delivery may aggravate cardiac dysfunction in women with significant underlying cardiac disease.

### Conditions Associated with High Risk of Maternal Complications during Pregnancy

Congenital heart disease is becoming more prevalent in women of childbearing age as a result of improved diagnostic modalities and reparative techniques.<sup>(33)</sup> Furthermore, acquired heart disease has become more prevalent now that many women are postponing pregnancy until later ages when the risk of cardiovascular disease is increased due to hypertension (HTN), diabetes, and obesity, 13% of pregnancies were complicated by primary cardiac events, defined as pulmonary edema, arrhythmia, stroke, or cardiac death.<sup>(34)</sup> The predictors of cardiac events were prior cardiac events or arrhythmias, poor functional class (or cyanosis, left heart obstruction (mitral valve area <2 cm<sup>2</sup>, aortic valve area <1.5 cm<sup>2</sup>, or peak left ventricular [LV] outflow gradient >30 mmHg), and LV dysfunction defined as LV ejection fraction (EF) <40%. It is therefore imperative that women with both acquired and congenital cardiac conditions be counseled about avoiding pregnancy and be evaluated and monitored if they become pregnant.

### Diagnosis of cardiovascular disease in pregnancy

A complete medical history is essential, focusing on characterization of the symptoms and signs associated with the physiological changes of pregnancy. Healthy pregnant women may present exertional dyspnea, fatigue and palpitations. On physical examination, lower limb edema and jugular venous distension are common findings. On cardiac auscultation, after the first trimester the first sound is louder, and an ejection systolic flow murmur, a third sound and an atrioventricular diastolic flow murmur are heard in 90%, 80% and 20% of cases, respectively.<sup>(37)</sup> However, chest pain, new-onset dyspnea, symptomatic hypotension, unexplained tachycardia,

palpitations associated with syncope, and cyanosis should be always considered warning signs. Differential diagnosis should be based on a detailed clinical history, with additional examinations being ordered according to clinical suspicion. Natriuretic peptides are maintained during pregnancy, and they have been shown to help exclude heart disease in pregnant women. However, changes in B-type natriuretic peptide levels in pregnancy, and their prognostic impact, and Their prognostic impact in pregnant women with heart disease, remain the subject of debate.<sup>(38)</sup>

The majority of pregnant women have a normal electrocardiogram (ECG), but elevation of the diaphragm by the pregnant uterus can lead to left axis deviation of 15-20°. Other possible non-pathological electrocardiographic findings are transient ST-segment and T-wave changes, presence of a Q wave and inverted T waves in DIII, an attenuated Q wave in aVF, and inverted T waves in V1, V2 and, occasionally, V3.<sup>(39)</sup> Transthoracic echocardiography (TTE) is the gold standard for assessing cardiac function during pregnancy. Non-pathological findings in a pregnant woman include mild dilatation of all four chambers (which may be more marked in the right atrium and ventricle), transient trivial mitral regurgitation (MR), physiological pulmonary and tricuspid regurgitation (TR), and increases in CO and left and right ventricular mass.<sup>(40)</sup> Aortic regurgitation (AR) is always pathological.<sup>(41)</sup> Transesophageal echocardiography can be useful for the characterization of CHD and when aortic dissection or prosthetic valve dysfunction are suspected, particularly for diagnosing vegetation and thrombi. If examinations involving ionizing radiation are called for, this decision requires careful consideration, because even though the priority is the mother's health, the effects on the fetus must also be taken into account. The radiation dose to which the fetus, which is protected by the uterus, is exposed tends to be lower than that received by the mother, although the fetus is more sensitive. The effects depend on the radiation dose and on gestational age; if possible, the exam should be postponed until after the first 12 weeks of pregnancy, the period of major organogenesis. There is no evidence that doses of <50 mGy are associated with increased risk of miscarriage, congenital malformation, growth restriction or mental problems. The dose to which a fetus is exposed from a chest X-ray is <0.01 mGy, but even so, an X-ray should only be performed if no other examination can clarify the etiology of the mother's symptoms. Computed tomography is rarely used for diagnosis of CVD in pregnancy and, given the high radiation doses required, is not recommended. Cardiac magnetic resonance imaging (MRI) appears to be safe for both mother and fetus.<sup>(42)</sup> And can be useful for characterizing complex heart disease and disease of the aorta. The risk to the fetus from exposure to gadolinium is not known and gadolinium contrast should therefore not be used.

Stress testing, either exercise or pharmacological, should also be avoided in pregnancy due to the risk of hypoxemia, fetal bradycardia and even fetal loss, caused by reduced placental blood flow. Pre-conception stress testing plays an important role in assessing functional capacity, chronotropic and blood pressure response to exertion, and exertion-induced arrhythmias in the monitoring of patients with CHD and asymptomatic valve disease. Stress echocardiography can be useful for pre-conception assessment of myocardial contractile reserve in women with previous PPCM and recovery of left

ventricular ejection fraction (LVEF), other cardiomyopathies with slightly impaired LVEF, valve disease, and CHD.<sup>(40)</sup>

### **Risk stratification of pregnant women with cardiovascular disease**

Assessment of the risk of pregnancy in women with known CVD should be individualized and ideally performed before pregnancy, including adjustments to medication such as suspending contraindicated drugs and introducing alternatives. Several scores have been created to stratify the risk of cardiovascular complications in pregnancy, the most commonly used of which is the Cardiac Disease in Pregnancy (CARPREG) risk score.<sup>(41)</sup> The European Society of Cardiology (ESC) guidelines recommend assessment of the risk of cardiovascular complications based on the classification of the World Health Organization (WHO), as this includes predictors that are not incorporated in the CARPREG and other risk scores.

### **Modified World Health Organization classification of maternal cardiovascular risk: principles (adapted from Regitz-Zagrosek).<sup>(39)</sup>**

- Risk of pregnancy by medical condition class
- No detectable increased risk of maternal mortality and no/mild increase in morbidity.
- Small increased risk of maternal mortality or moderate increase in morbidity.
- Significantly increased risk of maternal mortality or severe morbidity. Expert counseling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring is needed throughout pregnancy, childbirth and the puerperium.
- Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III.

### **Most common heart disease in pregnancy**

- Acquired valvar disease (mitral stenosis).
- Congenital heart disease (atrial septal defect).
- Cyanotic congenital heart disease (fallout's tetralogy).

### **Clark's classification of heart disease in pregnancy**

- **Group 1 minimal risk (mortality 0-1%)**
- (ASD, VSD, PDA) congenital heart disease.
- Fallout tetralogy (corrected).
- Any disease involving pulmonary and tricuspid valve.
- Bio prosthetic valve replacement.
- Mitral stenosis belonging to class 1, 2 according to Nyah.

### **Group 3 (mortality 25-50%)**

- Pulmonary hypertension.
- Primary or secondary an example of secondary being Eisenmenger syndrome.
- Marfan syndrome with aorta involvement >40mm.
- Coarctation of aorta.

Since group 3 maternal mortality is high these are also the indication of termination of pregnancy in heart disease patients

or they are the condition of heart disease in which pregnancy is contraindicated.

### NYHA Classification

- Class 1 no limitation of physical activity.
- Class 2 slightly limitation of physical activity.
- Class 3 marked limitation of physical activity.
- Class 4 severely compromised inability to perform any physical activity.

### Classification of Heart Disease according to etiology

- Cyanotic Congenital – non cyanotic.
- (ASD, VSD, Pulmonary stenosis, coarctation of aorta).
- Tetralogy of fallot and Eisenmenger syndrome.
- Rheumatic heart disease – MS, MR, AS, AR.
- Cardiomyopathy.
- Ischemic heart disease.
- Others – conduction defects, syphilitic, thyrotoxic, hypertensive.

### Conditions in which pregnancy risk is WHO I

- **WHO I. Uncomplicated, small or mild:**
- Pulmonary stenosis, Patent ductus arteriosus, Mitral valve prolapse.
- Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage).
- Atrial or ventricular ectopic beats, isolated.

### Conditions in which pregnancy risk is WHO II or III

- WHO II (if otherwise well and uncomplicated).
- Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot
- Most arrhythmias.

### WHO II-III depending on individual

- Mild left ventricular impairment.
- Hypertrophic cardiomyopathy.
- Native or tissue valve heart disease not considered WHO I or IV Marfan syndrome without aortic dilatation.
- Aorta <45 mm in aortic disease associated with bicuspid aortic valve Repaired coarctation.

### WHO III

- Mechanical valve
- Systemic right ventricle
- Fontan circulation
- Cyanotic heart disease (unrepaired)
- Other complex congenital heart disease
- Aortic dilatation of 40-45 mm in Marfan syndrome
- Aortic dilatation of 45-50 mm in aortic disease associated with bicuspid aortic valve

### Conditions in which pregnancy risk is WHO IV (pregnancy contraindicated)

- Pulmonary arterial hypertension of any cause

- Severe systemic ventricular dysfunction (LVEF <30%, NYHA III-IV)
- Previous peripartum cardiomyopathy with any residual impairment of left ventricular function severe mitral stenosis, severe symptomatic aortic stenosis
- Marfan syndrome with aorta dilated >45 mm
- Aortic dilatation of >50 mm in aortic disease associated with bicuspid aortic valve native severe coarctation.

### Congenital defects

- **Atrial septal defects (ASDs)** are one of the most common CHDs in pregnancy. ASDs may be newly diagnosed in pregnancy because the hemodynamic changes exaggerate right ventricular (RV) volume and may unmask an undiagnosed ASD. <sup>(43,44,45)</sup> Unrepaired (mWHO Class II) or repaired (mWHO Class I), ASDs are usually well tolerated in pregnancy unless associated with cyanosis or pulmonary hypertension. Women are at a <5% risk of arrhythmias, which occur more frequently in those with unrepaired shunts or those with shunts repaired at older ages. There is also a small risk of paradoxical emboli; thus, any signs of deep venous thrombosis should be investigated. Aspirin should be considered after 12 weeks because there is an increased rate of preeclampsia. Other complications include SGA and higher fetal or perinatal mortality. Rarely will ASD closure be required during pregnancy unless cyanosis occurs without significantly elevated pulmonary vascular resistance. Similarly, women with repaired small ventricular septal defects (VSDs) or small patent ductus arteriosus without an increase in pulmonary vascular resistance tolerate pregnancy well. Vaginal delivery is usually well tolerated with a consideration for IV air filters to prevent air embolisms. If an ASD or other shunt results in Eisenmenger syndrome (i.e., irreversible pulmonary vascular disease with reversal of the shunt direction and cyanosis; mWHO Class IV), maternal mortality has been reported to be as high as 20– 50%. These individuals should be counseled strongly against pregnancy and, if needed, should undergo early termination.<sup>8</sup> If resting arterial oxygen saturation is <85%, the likelihood of a live birth is 12%. Pregnant women with Eisenmenger syndrome or cyanotic heart disease should be referred to advanced CHD centers for further care given their significant morbidity and mortality risk.

- **Ventricular septal defect (VSD)** is commonly encountered as an isolated defect. As a rule, large defects lead to significant LV volume overload and heart failure early in life and are generally repaired in childhood. As a result, most unrepaired defects encountered in the adult population are small. In a large, multicenter retrospective cohort study, eighty-eight women were identified who had experienced 202 pregnancies, including 46 miscarriages and nine terminations of pregnancy. 104 completed pregnancies occurred in patients with unrepaired VSD, while 43 occurred in patients with repaired VSD. <sup>(46)</sup> The only cardiac complication was a single case of infective endocarditis that occurred in a patient with an unrepaired membranous VSD. Pre-eclampsia was more common in women with an unrepaired VSD compared with controls (OR 4.59, 95% CI 2.01–10.5). Interestingly, women with repaired VSD had a higher risk of premature labor (OR 4.02, 95% CI 1.12–14.4) than women with unrepaired VSD. Taken together, these data suggest that isolated VSD

imposes a low risk for cardiac complications during pregnancy.

- **Eisenmenger syndrome** poses a high risk to the mother and the fetus, with a reported maternal death rate of 40–50% and a miscarriage rate of 30%.<sup>(47)</sup> Patients should be counseled strongly not to become pregnant and a non-hormonal birth control option should be offered. If pregnancy occurs, elective early-term termination should be offered. Patients who elect to continue pregnancy should be monitored very carefully. Bed rest and gentle diuresis for right heart failure may be necessary. The systemic vasodilation of pregnancy may increase the magnitude of the right-to-left shunt. Measures to counteract this effect include supplemental oxygen and pulmonary vasodilators. However, there are no data to prove that these measures reduce the risk of death. Anticoagulation with heparin is often prescribed because of the risk for pulmonary arterial thrombosis. However, the benefit of this intervention must be weighed against the risk of pulmonary hemorrhage.
- **Tetralogy of Fallot (TOF)** is the most common cyanotic congenital cardiac defect in humans. The vast majority of adult patients with TOF will have had intracardiac repair consisting of a ventricular septal defect patch and enlargement of the RV infundibulum. This latter procedure is associated with a high incidence of pulmonic insufficiency, particularly when a transannular patch is used. This results in RV volume overload and enlargement which may confer an increased risk of right heart failure and arrhythmias during pregnancy.<sup>(48)</sup> A study of 112 pregnancies in 42 women with TOF suggested generally favorable outcomes: There were no maternal deaths, only one premature delivery, and 6 patients with repaired TOF (7%) reported cardiovascular complications during pregnancy. On the other hand, the rate of miscarriage was high: only 82 of the pregnancies were successful and 5 live-born infants (6%) were found to have congenital anomalies. Two smaller studies revealed similar results. Observational studies have suggested that maternal and fetal risks are highest in patients with severe pulmonic regurgitation and with RV systolic dysfunction. If possible, these patients should be evaluated completely before pregnancy and pregnancy should be delayed if pulmonic valve replacement is indicated.<sup>(49)</sup>

- **Valvar heart disease**

Stenotic and left-sided valve lesions are at higher risk of decompensation in pregnancy than regurgitate and right-sided lesions. Valve stenosis restricts increases in CO, raising transvalvular gradients and pressures upstream of the lesion, and is therefore less well tolerated in pregnancy than regurgitation, since regurgitate volume diminishes with systemic vasodilation and consequent reduced afterload. Mechanical heart valves are associated with specific problems (see below). Although most women with less severe valve disease tolerate pregnancy well, some valve lesions are considered prohibitive: severe MS, severe symptomatic aortic stenosis (AS), and any valve disease associated with LV dysfunction (LVD) and/or pulmonary hypertension (PH). Women with these conditions should receive pre-conception counseling and should be treated before pregnancy. Hemodynamic changes in pregnancy can lead to increased mitral and aortic valve gradients on TTE, leading to

overestimation of the severity of the valve lesion,<sup>(50)</sup> and so stenosis should be quantified by valve area assessed using planimetry, or by pressure half-time for MS or by the continuity equation for AS.<sup>(51,52)</sup> For women who remain stable during pregnancy, term delivery is recommended. Vaginal delivery with good pain management is the preferred method for most women with valve disease. Some experts suggest a cesarean section for patients with severe AS.

- **Pulmonary stenosis**

Isolated pulmonary stenosis is more common when there are congenital abnormalities of the pulmonary valve. Even in women with severe pulmonary stenosis, cardiac complications (HF and low CO) during pregnancy are rare, but if present they can be treated by percutaneous valvuloplasty, with good results at any gestational age.<sup>(53)</sup> Non-cardiac complications have been reported, including hypertensive disorders, prematurity and thromboembolic complications.<sup>(54)</sup>

- **Tricuspid regurgitation**

The causes of primary, non-trivial, TR in young women include CHD (for example Ebstein's anomaly, which, depending on its complexity, can affect the prognosis), rheumatic valve disease, and infective endocarditis. TR is usually well tolerated during pregnancy. However, in surgically corrected or uncorrected CHD in which the tricuspid is the only atrioventricular valve, the valve becomes regurgitate and may be associated with ventricular dilatation and dysfunction, which increases the pregnancy risk.<sup>(55)</sup>

- **Prosthetic valves**

When a woman who may become pregnant has a native valve replaced, the risks and benefits of a biological valve (risk of structural deterioration and less durability, with 90% likelihood of intervention for valve replacement after 15 years,<sup>(56)</sup> but with no need for anticoagulation need to be weighed against those of a mechanical valve (greater durability and better hemodynamic profile, but higher risk of thromboembolism and consequent need for lifelong anticoagulation). Pregnancy is usually well tolerated in women with biological valves; maternal cardiovascular risk depends on valve and ventricular function to a similar extent to native valve disease. Monitoring of the pregnancy is similar to that for native valve disease. The risk of valve thrombosis, bleeding and fetal complications is higher with mechanical valves.

A retrospective study published in 2015 of 84 pregnant women with valve disease (23 of whom had prosthetic valves) demonstrated that pregnancy in women with prosthetic valves was associated with high maternal and fetal morbidity.<sup>(57)</sup> 2015 also saw publication of data on the outcomes of pregnancy in women with prosthetic valves from the ESC's Registry of Pregnancy and Cardiac Disease (ROPAC).<sup>(58)</sup> This registry included 212 patients with mechanical valves, 134 with biological valves and 2620 without a prosthetic valve. Maternal mortality was 1.5% in the group with prosthetic valves and 0.2% in women without ( $p=0.025$ ). Valve thrombosis occurred in 10 women with mechanical valves, and bleeding complications were also more common in this group (23% vs. 5% both in women with biological valves and in those without a prosthetic valve,  $p<0.001$ ). Event-free survival was 78% in women without prosthetic valves, 79% in those

with biological valves and only 58% in those with mechanical valves ( $p=0.001$ ). Furthermore, fetal outcomes of mothers with mechanical valves were worse, with significantly higher incidences of miscarriage, death and lower birthweight. Many specialists therefore prefer to replace the native valve with a biological valve in women who wish to become pregnant, not only because of the lower associated risk, but also because studies have demonstrated that pregnancy does not affect degeneration of biological valves.<sup>(59)</sup> And because they permit percutaneous valve-in-valve treatment, which is likely to be required for intermediate- and high-risk patients in the future.

- **Mechanical valve**

The presence of a mechanical valve is an independent risk factor of complications. The balance between thrombotic and bleeding risks determines the chance of a successful uncomplicated pregnancy, which was about 57% in a large registry of women with a mechanical valve prosthesis.<sup>(60)</sup> A valve thrombosis occurred in 4.7%, and 20% of these women died. Anticoagulation strategies are predefined in the ESC guidelines, but a broad spectrum of regimes used globally, emphasizes the difficulty of anticoagulation management. In women who are not on low-dose vitamin K antagonists, a switch to some type of heparin in the first trimester is advised, due to the teratogenicity of vitamin K antagonists. To limit the risk of thrombosis with heparin. Women should be switched back to a vitamin K antagonist at the start of the second trimester, until the 36th week. A plan for heparin prescription around delivery should be ready. However, still there is no clear consensus on the best anticoagulation regime.<sup>(61,62)</sup>

- **Mitral stenosis**

MS is the most common valve disease in women of child-bearing age, and in 90% of cases is of rheumatic etiology. The hemodynamic changes associated with pregnancy (higher HR, CO, plasma volume and red blood cell mass) lead to increased left atrial pressure and PE. Many patients with MS become symptomatic for the first-time during pregnancy. The most common complications are reduced functional capacity, arrhythmias (most often atrial fibrillation [AF]) and PE. These are related to mitral valve area and NYHA class<sup>(63)</sup> and occur more often in the second and third trimesters, when hemodynamic changes are more marked.<sup>(64,65)</sup> If symptoms occur, the patient should be started on beta-blockers, to prolong ventricular filling time and reduce left atrial pressure, and, if necessary, diuretics to relieve congestion. Anticoagulation is indicated in the presence of AF, atrial thrombi or a history of thromboembolism. Percutaneous mitral commissurotomy should be considered only when, despite medical treatment, the patient remains in NYHA class III/IV, and preferably not until after 20 weeks gestation. Cardiac surgery should be reserved for life-threatening situations in which all other measures have failed.

- **Mitral regurgitation**

The most common causes of MR in pregnant women are rheumatic valve disease, MVP and CHD. Reduced PVR and BP during pregnancy explain why women with mild, moderate or even severe MR but without LV dilatation or dysfunction tolerate pregnancy well. However, increased plasma volume and CO can lead to HF or arrhythmias, particularly in cases of severe MR and in patients with LV dilatation or dysfunction.<sup>(50)</sup>

- **Complex congenital heart disease**

CHD accounts for 80% of heart disease in pregnant women in the Western world.<sup>(65)</sup> Some categories of CHD, such as Fontan circulation, systemic right ventricle and uncorrected cyanotic CHD, are associated with high maternal and fetal risk. In patients with Fontan circulation, 10% of pregnancies are associated with maternal complications, the most common of which are arrhythmias, and there may also be thromboembolic complications and worsening of HF.<sup>(66,67)</sup> There is agreement that Fontan patients with impaired ventricular function, severe atrioventricular regurgitation and enteropathy should be counseled against pregnancy. 14 Women with a systemic right ventricle (following Mustard or Senning surgery or with congenitally corrected transposition of the great vessels) have a similar risk of cardiac complications (10-30%), and should be assessed before pregnancy. Pregnancy should be discouraged in the presence of severe right ventricular dysfunction or TR.<sup>(61)</sup> In uncorrected cyanotic CHD without PH, 32% of pregnancies are associated with complications, most often HF. Fetal outcome is directly related to the mother's oxygen saturation at rest ( $\leq 85\%$  saturation is associated with fetal survival of only 12 %).<sup>(68)</sup>

- **High risk characteristics**

- **Pulmonary arterial hypertension**

Pulmonary arterial hypertension is indicated as modified WHO class IV. It is associated with a substantial risk of heart failure, ventricular arrhythmias for the mother and also an increased mortality risk, although outcome seems to be better in the current era of advanced therapies. Poor outcome for the fetus is another reason to be very restrained with positive advice on pregnancy. It must be marked that evidence on outcome is limited. Maternal mortality varies from absolute high risk of 28%, to slight improvement in outcome in selected patients with congenital heart disease, but still a maternal mortality rate of 7%.<sup>(69)</sup> Counselling about the high-risk and thus absolute contraindication to pregnancy remains paramount. When women do become pregnant, options on termination should be given. Otherwise, a plan on strict follow-up, advanced therapy and delivery should be made in a multidisciplinary team with expertise in pulmonary hypertension. In case of Eisenmenger syndrome, there is also an absolute contraindication for pregnancy. Pregnancy-induced decrease in peripheral vascular resistance causes an additional risk of progressive right-to-left shunt, cyanosis and paradoxical emboli. Very poor fetal outcome can be expected in the majority of cases.<sup>(70)</sup>

- **Pulmonary hypertension**

PH is associated with high maternal mortality, but advances in pulmonary vasodilator therapy have raised hopes of improvements in prognosis.<sup>(71)</sup> Among types of PH, the best prognosis is seen with idiopathic PH under specific therapy, for which mortality is 9%.<sup>(72)</sup> In this group, women with Vaso-reactive PH who are stable under calcium channel blocker therapy have a relatively good prognosis during pregnancy.<sup>(73)</sup> Despite improvements in prognosis for women with PH in recent decades, this condition is still associated with high mortality, and is categorized as risk level IV in the WHO classification. No criteria have been agreed for identifying women with lower risk during pregnancy<sup>(50)</sup>, and all women diagnosed with PH are advised not to become pregnant. If a



woman decides to continue with the pregnancy, she should be referred to a center specializing in PH and followed by a multidisciplinary team. Pulmonary vasodilator therapy in use before pregnancy should be continued, except for endothelin receptor antagonists (bosentan, macitentan and ambrisentan), which are teratogenic and should be replaced by sildenafil and/or prostacyclin derivatives.

- **Peripartum cardiomyopathy**

In 2010, the ESC's working group on PPCM proposed a simplified definition of this entity, as an idiopathic cardiomyopathy frequently manifested by HF secondary to LV systolic dysfunction (LVEF <45%) towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. <sup>(74)</sup> As there is as yet no specific examination for diagnosing PPCM, it is a diagnosis of exclusion and must be differentiated from existing heart failure decompensated by the hemodynamic changes underlying pregnancy. What little epidemiological information is available on this entity comes mainly from Nigeria, South Africa and Haiti, where its incidence is higher, and the US, where its incidence is increasing. <sup>(75)</sup> In 2017, Sliwa et al. published data gathered between 2012 and 2016 in the EURO observational Research Program <sup>(76)</sup> demonstrate that PPCM occurs in women from all over the world, with different ethnic origins and socioeconomic conditions, but with very similar forms of presentation and course. Risk factors that have been identified are African-American descent, older maternal age multifetal pregnancies and hypertensive disorders during pregnancy.

Although its etiology remains unknown, various mechanisms have been suggested, such as low selenium levels, reactivation of latent viral infections, stress-activated cytokines, inflammation, autoimmune reactions, pathological response to hemodynamic stress and unbalanced oxidative stress. <sup>(77)</sup> Recently a new potentially causal factor has been described, cleavage of prolactin to produce a 16-kDa N-terminal prolactin fragment (16K PRL), mediated by oxidative stress. <sup>(78)</sup> The antiangiogenic effect of 16K PRL and of soluble fms-like tyrosine kinase-1 (sFlt-1), levels of which are also high in this condition, can change the balance of angiogenesis, leading to vascular damage and hence HF. <sup>(79)</sup> The high incidence of PPCM in Africans and a family history in 16% of cases have suggested a possible genetic cause, but the mutations documented so far are associated with familial forms of cardiomyopathy.

The majority of patients admitted with PPCM have typical symptoms and signs of HF. Differential diagnosis should be made with other entities including myocarditis, pre-existing cardiomyopathy, valve disease and congenital heart disease. When presentation is with cardiogenic shock, myocardial infarction and pulmonary embolism should immediately be excluded. An ECG should be performed in all patients suspected of having PPCM, even though there is no specific electrocardiographic pattern, due to its high negative predictive value. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are usually high and can be used to exclude non-cardiac-related dyspnea, although it does not help differentiate PPCM from other cardiomyopathies. TTE should be performed as soon as possible in all cases of suspected PPCM, to exclude other heart disease and complications such as apical thrombus, and to obtain prognostic information. Although prognosis is more favorable in PPCM than in other cardiomyopathies, it is

associated with significant mortality (<5-50%) and morbidity (PE, cardiogenic shock, arrhythmias and thromboembolic events). Mortality risk is higher with advanced maternal age, multiparity, severely impaired global systolic function, African-American race and late diagnosis. The proportion of patients who recover left ventricular function (LVEF  $\geq$ 50%) varies according to the study (35-70%), but in most cases this occurs within six months of childbirth. Recent studies show that African-American race and lower LVEF and greater LV end-diastolic volume at diagnosis are associated with a lower probability of recovery. <sup>(80)</sup> In subsequent pregnancies, women with persistent LVD are at greater risk (around 50%) of clinical deterioration than those with complete recovery of ventricular function, although in the latter there may be recurrence in another pregnancy (cardiac function worsens in around 20%, in 20-50% of whom this persists following delivery). <sup>(81)</sup>

From a therapeutic standpoint, the approach to PPCM is similar to that of other causes of acute HF, taking care to avoid adverse effects on the fetus. A proposed treatment algorithm, according to the patient's hemodynamic stability. In hemodynamically unstable patients a rapid and systematic approach is essential in order to provide support and prevent target organ damage. This is one of the few situations in which an emergency cesarean section is indicated to treat the mother, with the aim of starting bromocriptine. <sup>(82)</sup> Regarding inotropic support, levosimendan is preferred in these patients as it does not increase myocardial oxygen consumption, while catecholamines should be avoided. If levosimendan is unavailable, dobutamine is the inotrope of choice, and noradrenaline should be used as a vasopressor agent. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers and renin inhibitors are contraindicated during pregnancy due to their fetal toxicity. Alternatively, nitrates and hydralazine can be used to reduce pre- and afterload, respectively. After childbirth, ACEIs can be resumed, preferably captopril and enalapril during breastfeeding. While beta-blockers increase the risk of intrauterine growth restriction, they can be used in hemodynamically stable patients, preferably beta 1 selective beta-blockers such as metoprolol succinate. Mineralocorticoid receptor antagonists should be avoided in pregnancy and breastfeeding. Bromocriptine, in association with HF therapy, should be considered in view of its promising results in terms of recovery of LV systolic function and clinical improvement. <sup>(83)</sup> In a German retrospective registry of PPCM, treatment with beta-blockers, ACEIs and bromocriptine (2.5 mg twice daily for two weeks followed by 2.5 mg once daily for six weeks) was associated with favorable outcomes. <sup>(84)</sup> Anticoagulation with heparin should be started in patients with PPCM under bromocriptine and/or with LVEF  $\leq$ 35% (during pregnancy and for at least eight weeks after delivery). <sup>(85,86)</sup> Treatment to counteract ventricular remodeling should be continued for at least 12 months after recovery of LV dimensions and function. Although the main cause of death in PPCM is HF, one quarter of deaths occur due to ventricular arrhythmias, most in the first six months. <sup>(87)</sup> The use of wearable cardioverter-defibrillators for six months after diagnosis of PPCM has been proposed for women with severe LV dysfunction, as a bridge to recovery of LV function or placement of an implantable cardioverter-defibrillator.

- **Eisenmenger syndrome** <sup>(88)</sup>

Described a large ventricular septal defect as well as the pathological features of PAH. In 1958, Wood expounded this

syndrome as a result of an increased pulmonary vascular resistance (PVR)  $> 800$  dynes/sec/cm<sup>5</sup> with a reversed or bidirectional shunt through a large ventricular septal defect. Eisenmenger syndrome is very rare in pregnant women with an incidence of about 3% in the pregnant patients with congenital heart defects. Nevertheless, debates remain concerning the management of Eisenmenger syndrome in this patient population and the prognosis is unclear in terms of maternal and fetoneonatal outcomes.

#### • Aortic dilatation

Women with aortic disease may face the risk of further dilatation, or worse, dissection during pregnancy. The extent of diameter growth during pregnancy is difficult to predict and the results diverge between no significant growth up to 3 mm growth during the entire pregnancy with potential decrease of diameter after pregnancy.<sup>(89,90,91)</sup> The risk of dissection depends on the underlying syndrome, as it does outside pregnancy. Hence, women with Marfan syndrome and Loeys-Dietz syndrome are at highest risk. In the absence of Marfan syndrome or other high-risk heritable thoracic aortic disease (HTAD), a cut-off of 50 mm, also in the presence of a bicuspid valve is used to advise against pregnancy. In Marfan syndrome and Loeys-Dietz syndrome or other HTAD, women should not embark on pregnancy in the presence of an aortic root diameter  $>45$  mm.<sup>3</sup> In Turner syndrome, diameters specifically need to be corrected for body surface area, and a threshold of 27 mm/m<sup>2</sup> is adopted.<sup>(92)</sup> Elective surgery in women beyond these thresholds may be considered, however the risk of type B dissection and other complications is still not zero after surgery. Risk factors such as (family) history of dissection also need to be taken into account. A caesarean section is advised in all women with an aortic root diameter  $>45$  mm. Below 40 mm, a vaginal delivery is considered safe. Between 40 and 45 mm the choice may depend on diameter growth during pregnancy and risk factors for dissection.<sup>(92)</sup>

#### • Aortic stenosis

Bicuspid aortic valve is the main cause of AS in women of child-bearing age, and is frequently associated with aortic dilatation and coarctation, which further increases the risk in pregnancy. Mild to moderate AS is generally well tolerated, unlike severe AS, which is associated with angina, tachyarrhythmias and PE. Unlike MS, there is no effective pharmacological therapy for AS. Pulmonary congestion can be relieved with diuretics, although these should be avoided as much as possible due to the risk of hypotension and reduced placental blood flow. Where there are signs and symptoms of HF, syncope or angina, percutaneous or surgical intervention is indicated.<sup>(51)</sup>

#### • Aortic regurgitation

Like AS, the most common cause of AR in young women is bicuspid aortic valve. Women with severe AR and preserved systolic function usually tolerate pregnancy well. However, severe AR associated with LVD due to increased CO and plasma volume is poorly tolerated. Symptomatic pregnant women should receive HF therapy. Coarctation of the aorta accounts for 6–8% of the patients with congenital heart disease. Most females born with aortic coarctation are expected to reach childbearing age with a previous history of surgical repair.<sup>(50)</sup>

Coarctation of the aorta is a birth defect in which a part of the aorta is narrower than usual. If the narrowing is severe enough and if it is not diagnosed, the baby may have serious problems and may need surgery or other procedures soon after birth. For this reason, coarctation of the aorta is often considered a critical congenital heart defect. The defect occurs when a baby's aorta does not form correctly as the baby grows and develops during pregnancy. The narrowing of the aorta usually happens in the part of the blood vessel just after the arteries branch off to take blood to the head and arms, near the patent ductus arteriosus, although sometimes the narrowing occurs before or after the ductus arteriosus. In some babies with coarctation, it is thought that some tissue from the wall of ductus arteriosus blends into the tissue of the aorta. When the tissue tightens and allows the ductus arteriosus to close normally after birth, this extra tissue may also tighten and narrow the aorta.

#### • Pre-delivery management

In an ideal world, all women of reproductive age with congenital or acquired heart disease should have access to specialized multidisciplinary preconception counselling in order to empower them to make choices about pregnancy. Once they are pregnant, all women with heart disease should be assessed clinically as soon as possible by a multidisciplinary team and appropriate investigations undertaken. The core members of the team should include suitably experienced obstetricians, cardiologists, and anaesthetists; but midwives, neonatologists, and intensivists should also be involved in planning, when appropriate. Suitable arrangements for care should then be made at a district general hospital or tertiary unit according to the complexity of the heart disease, the risk assessment, and the locally available facilities and expertise.<sup>(93)</sup> A clear plan for the management of labour and the puerperium in women with heart disease should be established in advance, well documented, and distributed widely (including to the woman herself) so that all personnel likely to be involved in the woman's intra- and post-partum care are fully informed.

The main aims of management are: to optimize the mother's condition during the pregnancy (e.g., considering  $\beta$ -blockers, thromboprophylaxis, or pulmonary arterial vasodilators in appropriate cases); to monitor for deterioration; and minimize any additional load on the cardiovascular system from delivery and the post-partum period. Women with heart failure can be safely treated with diuretics, digoxin, and hydralazine, nitrates, or both as vasodilators to offload the left ventricle.<sup>(94)</sup> Additional fetal assessments may be needed in order to monitor for potential problems arising from pharmacological treatment of the mother. Potential fetal effects arising from cardiovascular drugs during pregnancy.

#### • ACE-inhibitors

- Avoid in all trimesters if possible
- Skull defects.
- Oligohydramnios
- May adversely affect fetal and neonatal arterial pressure control and renal function.

#### • Warfarin

- Teratogenic in first trimester.
- Risk of fetal hemorrhage.
- Increased risk miscarriage and stillbirth.

- **$\beta$ -blockers**
- May cause intra-uterine growth restriction, neonatal hypoglycemia, and bradycardia.
- **Sildenafil**
- Toxicity in animal studies
- No reports of toxicity in humans
- **Diuretics**
- Thiazides in the third trimester may cause neonatal thrombocytopenia.
- **Digoxin**
- No reports of harm to fetus
- May need dosage adjustment
- **Hydralazine**
- No reports of serious harm in third trimester
- Manufacturer advises avoid in first and second
- **Low molecular weight heparin**
- Not known to be harmful to fetus.
- **Unfractionated heparin**
- Not known to be harmful to fetus.
- **Calcium-channel blockers**
- Uterine relaxation so may inhibit labour.
- **Diltiazem**
- Should be avoided.
- **Verapamil**
- May reduce uterine blood flow.
- **Mode of delivery**

Vaginal delivery is the preferred mode of delivery for most women with heart disease, unless there are specific obstetric indications or a deterioration in cardiac performance necessitating early delivery. The rate of Caesarean section is much higher for women with heart disease compared with the general population for this reason. In most cases, vaginal delivery is best achieved by aiming for spontaneous onset of labour, providing effective pain relief with low-dose regional analgesia and, if necessary, assisting vaginal delivery with instruments such as the ventouse or forceps, in order to limit or avoid maternal effort in 'pushing'. Regional analgesia during labour is usually recommended in order to reduce the further increases in cardiac output and myocardial oxygen demand caused by pain and anxiety. Good regional analgesia will also facilitate instrumental delivery. Induction of labour may be appropriate in order to optimize the timing of delivery in relation to anticoagulation and availability of specific medical staff, or because of deteriorating maternal cardiac function.<sup>(94)</sup>

General and regional anesthesia (spinal, epidural, or combined spinal-epidural) have been used for Caesarean section. A recent 5 yrs. review of practice in an Australian hospital found that six of the seven parturient with NYHA grade IV symptoms received regional anesthesia (three for Caesarean section and three for labour,<sup>(95)</sup> and 12 out of 17 with NYHA grade III symptoms received regional anesthesia (six for Caesarean section and six for labour). There is no evidence to support any particular technique, but cardiovascular stability is the goal. It is recommended that if oxytocin is required post-delivery, it should only be administered by infusion with the omission of a bolus. It has been argued that the cardiovascular effects of a post-partum hemorrhage in a patient with a fixed cardiac output, and the potential risk of overzealous i.v. fluid replacement in response, are worse than the potential cardiovascular effects of a slow infusion of oxytocin.<sup>(96)</sup> (Which include peripheral vasodilation, tachycardia, and fluid

retention). Ergometrine should be avoided in severe cardiac disease as it leads to vasoconstriction and hypertension, and increases the risk of myocardial infarction and pulmonary oedema. Carboprost is not recommended in cardiac disease (see the British National Formulary) as it too has the potential to cause/exacerbate pulmonary oedema. It should also be noted that the use of a glyceryl trinitrate infusion post-delivery may improve pulmonary oedema; however, it may also increase the risk of post-partum hemorrhage due to uterine relaxation.

#### • **Post-partum**

In the post-partum period, high-level maternal surveillance is required until the main hemodynamic changes after delivery have resolved. For particularly unstable cardiac conditions, such surveillance may be required in hospital for up to 2 weeks. A recent review of parturient with heart disease found that the worst cardiac compromise did not always occur at the time of delivery. The occurrence of chest infection or development of peripartum cardiomyopathy (which may occur anytime from 1 month pre-delivery up to 5 months post-delivery) in some cases lead to worse compromise post-delivery.<sup>(95)</sup>

#### • **Contraception in heart disease**

- Contraception of choice Temporary IUCD (earlier IUCD was. Not recoded but now WHO recommend s its use) progesterone only pills, implant or injection, condoms
- Contraception to be avoided: OCPs (can precipitate thromboembolic event)
- Contraception of choice –permanent:
- If the heart is not well compensated, the patient's husband is advised for vasectomy.
- If heart is well compensated tubal sterilization can be carried out.
- Sterilization should be considered with the completion of the family at the end of first week in the puerperium under local anesthesia through abdominal route by mini lap technique.

#### • **Prognosis of heart disease in pregnancy**

- Highest mortality associated with class 3 of Clark s classification – Eismenger syndrome.
- Stenotic lesions have a higher mortality than regurgitate lesions.
- Aortic stenosis has higher mortality than > mitral stenosis > pulmonary. Congenital heart disease and mitral valve prolapse have least mortality.<sup>(97)</sup>

#### **Aim of the Study**

The aim of this to assess the prevalence of cardiovascular disease among pregnant women in Benghazi Medical center (BMC).

#### **MATERIALS AND METHODS**

This is a prospective study done at the department of obstetrics and gynecology at Benghazi Medical Center in Benghazi, Libya. The study was conducted between January 1, 2021, until January 31, 2022. During this time, all samples were collected and recorded using questionnaires and patient

consent forms, which were approved by the ethical committee of Benghazi Medical Center in Libya. The sample consisted of pregnant women with cardiac disease. The data obtained from the patient includes maternal medical conditions, pregnancy complications, mode of delivery (normal or caesarean section), perinatal and neonatal outcomes (Echo), and post-delivery complications. Demographic information includes maternal age, gravidity, parity, history of surgical procedures, pregnancy complications, including anemia, hypertension, preterm rupture of membrane, dyspnea, D.M., known congenital heart disease, and rheumatic heart disease. Perinatal and neonatal outcomes, including gestational age at delivery, preterm birth, and stillbirth Echo for the newborn

## RESULTS

**Table 1. Showing different age groups among the cases**

Age	No of cases	Percentage %
20 - 25	3	11.5
26 - 30	4	15.4
31 - 35	8	30.8
36 - 40	5	19.2
41 - 45	6	23.1
Total	26	100

8 patients of cases (30.8%) are between 31 and 35 years old, 6 patients (23.1%) are between 41 and 45 years old, 5 patients (19.2%) are between 36 and 40 years old, 4 patients (15.4%) are between 26 and 30 years old, and 3 patients (11.5%) are between 20 and 25 years old.

**Table 2. Showing the distribution of parity among cases of studied samples**

Parity	No of Cases	Percentage %
Primigravida	4	15.4
Multipara	19	73.1
Grand multipara	3	11.5
Total	26	100

Most of the patients are multipara (19 cases) (73.1%), 4 cases are primigravida (15.4%), and 3 patients (11.5%) are grand multipara.

**Table 3. Showing the mode of delivery among the cases**

Mode of Delivery	No of Cases	Percentage %
Normal vaginal delivery	4	15.4
Caesarean section	22	84.6
Total	26	100

Cardiac diseases increase the incidence of caesarean section, which 22 patients (84.6%) of patients delivered by caesarean section, while only 4 patients (15.4%) delivered normally.

**Table 4. Showing the indication of caesarean section among our cases**

Induction	No of cases	Percentage %
Previous (repeated) Caesarean	6	27.4
Fetal distress	3	13.6
Cardiac Problem	11	50
Twins	1	4.5
Placenta Previa	1	4.5
Total	22	100

The most prevalent cause of caesarean section is cardiac disease (50 %), followed by 6 patients (27.3 %) due to repeated caesarean sections, 3 patients (13.6 percent) due to fetal distress, and only one patient due to twins indication, as well only one patient due to placenta Previa.

**Table 5. Showing the type of cardiac diseases**

Type of cardiac disease	No of cases	Percentage %
Congenital	12	46.2
Acquired	14	53.8
Total	26	100

There are 12 patients (46.2 %) with congenital heart lesions, and 14 patients (53.8 %) with acquired cardiac disease among the patients.

**Table 6. Showing the type of congenital cardiac lesion among case**

Cardiac lesion	No of cases	Percentage %
Mitral stenosis	3	25
Mitral regurgitation	1	8.3
Tricuspid regurgitation	2	16.7
Aortic stenosis	2	16.7
Aortic regurgitation	1	8.3
Mitral valve prolapse	1	8.3
VSD (Ventricular septal defect)	1	8.3
Ebstein anomaly	1	8.3
Total	12	100

3 out of 12 patients with congenital heart disease have mitral stenosis (25%), 2 of patients (16.7%) have tricuspid regurgitation, 2 patients have Aortic stenosis (16.7%), one patient (8.3) has Aortic regurgitation, one patient (8.3%) has Mitral valve prolapse, one patient (8.3%) has Ventricular septal defect and one patient (8.3%) has Ebstein anomaly.

**Table 7. Showing the type of acquired cardiac disease.**

Cardiac disease	No of cases	Percentage %
Non-Rheumatic	13	93
Rheumatic	1	7
Total	14	100

Most of the acquired heart disease patients are non-Rheumatic 13 out of 14 (93%), and only one patient is Rheumatic heart disease (7%).

**Table 8. Showing the acquired cardiac disease diagnosis**

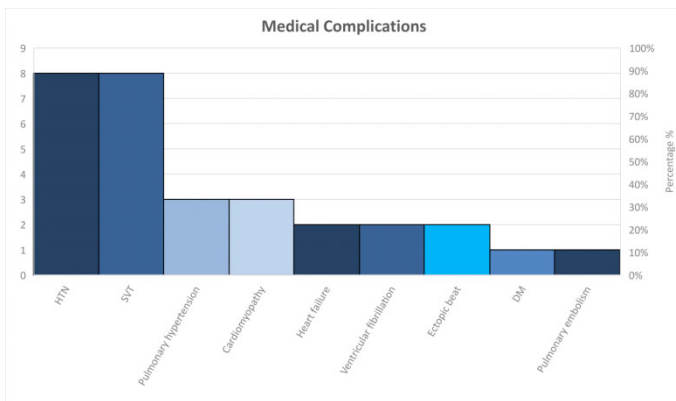
Cardiac disease	No of cases	Percentage %
SVT	7	50
Pulmonary Hypertension	2	14.3
Ectopic beat	1	7.1
Ventricular arrhythmia	1	7.1
Cardiomyopathy	1	7.1
Coronary heart disease	1	7.1
Rheumatic mitral regurgitation	1	7.1
Total	14	100

Most of the patients 7 patients (50%) were diagnosed with SVT, 2 patients (14.3%) with pulmonary hypertension, one patient (7.1%) with Ectopic beat, one patient (7.1%) with Ventricular arrhythmia, one patient (7.1%) with Cardiomyopathy, one patient (7.1%) with coronary heart disease, and one patient (7.1%) with Rheumatic mitral regurgitation.

**Table 9. Showing the medical complications occurring in the cases**

Complications	No of cases	Percentage %
HTN	8	30.8
SVT	8	30.8
Pulmonary hypertension	3	11.5
Cardiomyopathy	3	11.5
Heart failure	2	7.7
Ventricular fibrillation	2	7.7
Ectopic beat	2	7.7
DM	1	3.8
Pulmonary embolism	1	3.8

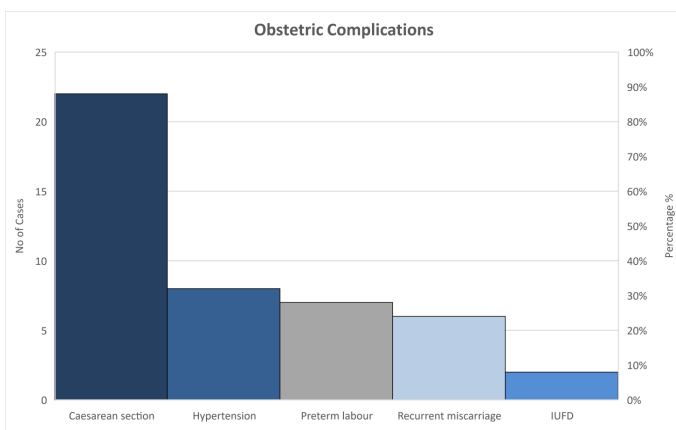
8 patients (30.8%) had SVT; 8 patients (30.8%) have hypertension accompanying the cardiac disease, 3 patients (11.5%) with pulmonary hypertension, 3 patients (11.5%) complicated by cardiomyopathy, 2 patients (7.7%) complicated by heart failure, 2 patients (7.7%) complicated by ventricular fibrillation, and just only one patient (3.8%) complicated by pulmonary embolism. There is a strong statistically significant link between cardiac disease and occurrence of medical complication during the pregnancy and delivery.



**Table 10. Showing the obstetric complication among the cases**

Obstetric complication	No of cases	Percentage %
Caesarean section	22	84.6
Hypertension	8	30.8
Preterm labour	7	26.9
IUFD	2	7.7
Recurrent miscarriage	6	23.1

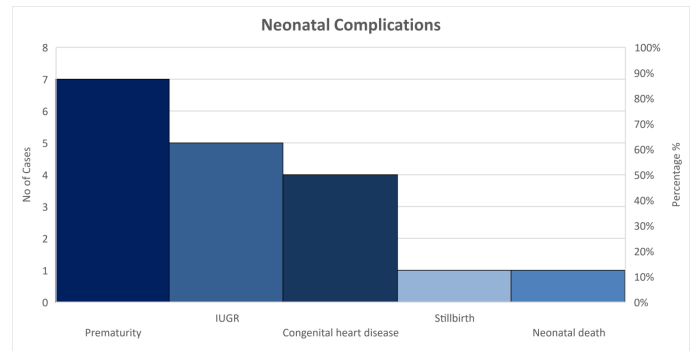
22 patients (84.6%) delivered by caesarean section, 8 patients (30.8%) having hypertension during the pregnancy, 7 patients (26.9%) delivered preterm, 2 patients (7.7%) delivered died baby (IUFD), and 6 patients (23.1%) have history of miscarriage recurrent. According to the statistic results finding, there is a strong correlation between cardiac disease and obstetric complication.



**Table 11. Showing neonatal complications**

Complication	No of cases	Percentage %
Congenital heart disease	4	15.4
Prematurity	7	26.9
IUGR	5	19.2
Stillbirth	1	3.8
Neonatal death	1	3.8

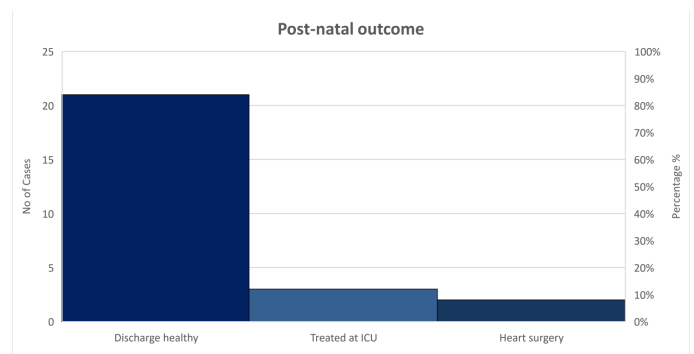
4 babies (15.4%) delivered have congenital heart disease, 7 babies (26.9%) premature, 5 babies (19.2) with IUGR, one baby (3.8%) stillbirth, and one baby (3.8%) died neonate. Statistically significant, there is a strong correlation between maternal cardiac disease and neonatal complications.



**Table 12. Showing post-natal outcome**

Post outcome	No of cases	Percentage%
Discharge healthy	21	80.7 %
Treated at ICU	3	11.6 %
Heart surgery	2	7.7 %
Total	26	100%

21 patients has no complication, and they discharged from the hospital within two days from the delivery date, 3 patients had transferred to the Intensive Care unit (ICU), and two patients had an open heart surgery after six months from the delivery date.



**DISCUSSION**

Cardiac disease is a leading cause of non-obstetric maternal death worldwide, but little known about its burden in Libya. This study had conducted to investigate the burden of cardiac disease in pregnancy in Libya, at Benghazi medical center (BMC) specifically. Included all patients presented to hospital to giving childbirth and they already diagnosed with some sort of cardiac problems. The study took a place during the period from January/2021 to January/2022, where the total number of delivery 14,593 births, and found 26 patients diagnosed by cardiac diseases out of the total number admitted during the time of our study. Which presented as 1:561 (one patient

diagnosed by cardiac disease among 561 patients). Regarding their age they distributed respectively (30.8%) are between 31 and 35 years old- (23.1%) are between 41 and 45 years old- (19.2%) are between 36 and 40 years old-(15.4%) are between 26 and 30 years old-and (11.5%) are between 20 and 25 years old. Most of our patients range below the 41 years old (76.9%), with Mean age of 32.9. in Rebecca Lumsden.... etc. <sup>(98)</sup> that conducted as a retrospective case-control study of pregnant women admitted to a national referral hospital in western Kenya between 2011–2016, <sup>(98)</sup> they found A total of 97 cardiac cases in pregnancy with median age of cardiac cases was 26 years. Parity had reported to play an important role in the development of cardiovascular disease. <sup>(99)</sup> Wenzhen Li.... etc. <sup>(99)</sup> meta-analysis of cohort studies, ten cohort studies involving 150,512 incident cases of cardiovascular disease among 3,089,929 participants were included in the meta-analysis. A significant association between parity and cardiovascular disease risk was observed while comparing parity with nulliparity, with a summarized relative risk of 1.14 (95% confidence interval (CI) 1.09–1.18;  $I^2 = 62.0\%$ ,  $P = 0.002$ .) ever parity is related to cardiovascular disease risk and there is an association between the number of pregnancies and the risk of cardiovascular disease. <sup>(99)</sup> In Rebecca Lumsden.... etc. <sup>(98)</sup> Nearly two-thirds (63.9%) of cardiac cases had a previous delivery, while 30% had three or more, gravidity (median range) 2 (1–8), Parity, (median range) 1 (0-8). Nulliparous, n (%) 35 )36.1(, Parity 1–2, n (%) 33 (34.0), Parity  $\geq 3$ , n (%) 29 (29.9). in Eva Furenäs.... etc. <sup>(91)</sup> In this largest analysis to date with a focus on parity in 307 women, the risk classification predicts the maternal outcome more than parity per se. If the first pregnancy is uneventful, the OR is 5.5 for an uneventful second pregnancy if CARPREG I and mWHO scores remain unchanged. <sup>(100)</sup>

In current study most of the patients are multipara (19 cases) (73.1%), 4 cases are primigravida (15.4%), and 3 cases (11.5%) are grand multipara. this means our results supported by previous ones. In Dan Zhu..... etc. <sup>(101)</sup> Independent from parity, the rate of impaired cardiac diastolic function was significantly higher in women of advanced age than that in women of young age. While in both subgroups of advanced age and young age, parity had no significant effect on the rate of impaired cardiac diastolic function. <sup>(101)</sup> We noticed with our participants that cardiac diseases increase the incidence of caesarean section (CS), 22 (84.6 %) of patients delivered by caesarean section, while only 4 patients (15.4%) delivered normally. The most prevalent cause of caesarean section is cardiac disease (50 %), followed by 6 patients (27.3 %) due to repeated caesarean sections, 3 patients (13.6 percent) due to fetal distress, and only two patients due to other indications. This high rate of CS may not have any clinically significant in aim to improve the maternal or fetal outcomes according to current evidence of data, in Titia P E Ruys ...etc. <sup>(102)</sup> The caesarean section was planned in 393 women (31%): 172 (44%) for cardiac and 221 (56%) for obstetric reasons of whom 53 delivered by emergency caesarean section. Vaginal delivery was planned in 869 (69%) women, of whom 726 (84%) actually delivered vaginally and 143 (16%) had an emergency caesarean section. These data suggest that planned caesarean section does not confer any advantage over planned vaginal delivery, in terms of maternal outcome, but is associated with an adverse fetal outcome. In Victoria Asfour ...etc. <sup>(103)</sup> (one hundred and nineteen studies were identified of these, 13 papers represented the best evidence) Vaginal birth is safe in patients with adult congenital heart disease (ACHD) of all

severities, and a higher CS rate does not translate into improved outcomes. The evidence suggests that a higher CS rate is in fact associated with an increased overall risk of adverse outcomes (including mortality) for the mother. <sup>(103)</sup> In fact, Cardiac diseases in pregnancy could divided into three main groups: Pre- existing disease. The disease antedates and is known before pregnancy, e.g., congenital heart disease or rheumatic heart disease; Disease that is first recognized or has its onset during pregnancy, e.g., myocardial infarction; and Pregnancy specific disease, e.g., peripartum cardiomyopathy. <sup>(104)</sup> Our participants there are 12 patients (46.2 %) with congenital heart lesions, and 14 patients (53.8 %) with acquired cardiac disease among the patients, the congenital cardiac lesion among cases represent as 3 out of 12 patients with congenital heart disease have mitral stenosis (25%), 2 of patients (16.7%) have tricuspid regurgitation, 2 patients have Aortic stenosis (16.7%), one patient (8.3) has Aortic regurgitation, one patient (8.3%) has Mitral valve prolapse, one patient (8.3%) has Ventricular septal defect and one patient (8.3%) has Ebstein anomaly. In Surabhi Nanda...etc. <sup>(105)</sup> they found in UK, the most common congenital heart diseases in pregnant women, which account for nearly 60% of cases, are patent ductus arteriosus (PDA), atrial septal defect (ASD) and ventricular septal defect <sup>(104)</sup>, PDA & ASD not represent in our study sample.

Regarding acquired cardiac disease mitral stenosis (MS) remains the most common important pre-existing heart condition in pregnancy worldwide, most of our participants with acquired heart disease are non-Rheumatic 13 out of 14 (93%), and only one patient is Rheumatic heart disease (7%), most of the patients, 7 patients (50%) were diagnosed with supraventricular tachycardia SVT, 2 patients (14.3%) with pulmonary hypertension, one patient (7.1%) with Ectopic beat, one patient (7.1%) with Ventricular arrhythmia, one patient (7.1%) with Cardiomyopathy, one patient (7.1%) with Coronary heart disease, and one patient (7.1%) with Rheumatic mitral regurgitation, these results may due to small sample size in short time duration, as its not going with evidence worldwide.

In a study conducted in England in 2002, mitral valve prolapse (MVP) was identified as the most common heart disease, which its common symptom is heart palpitations during pregnancy, and the patients have been treated with Inderal<sup>106</sup>. Rheumatic valvular stenosis still considered as the most common heart disease in the pregnant women in many countries, which manifested as mitral stenosis in 75% of the cases. <sup>(107)</sup> Therefore, heart rheumatism has been identified as one of the most common causes of valvular heart disease. Wang et al found that the prevalence of heart rheumatism is equal to 8/1000. Rheumatic heart disease is the most common cause of the existing valvular diseases in females in our country. MVP is often well-tolerated with treatment. <sup>(108)</sup> Congenital heart disease is the most common cause of heart damages in the pregnant women. <sup>(97)</sup> Thida Thanajiraprapa & Vorapong Phupong...etc. <sup>(109)</sup> rheumatic heart disease (RHD), congenital heart disease (CHD), arrhythmia and cardiomyopathy were observed in 133 (68.9%), 26 (13.5%), 32 (16.6%) and 2 (1%) cases, respectively. Obstetric complication was found in 27 (14%) cases that was composed of preterm delivery (11.4%), gestational diabetes (1%), pregnancy induced hypertension (1%) and postpartum hemorrhage (0.5%). Cardiac complication was observed in 24 (12.4%) cases. Congestive heart failure was the most common cardiac

complication, which observed in 11 (5.7%) cases. There were four (2.1 %) maternal deaths, three cases in CHD group and one case in RHD group. Preterm infant was observed in 22 (11.4%) cases. Thirteen percent had low birth weight and 8.3% were small for gestational age. There were no perinatal deaths or congenital anomalies. RHD with pregnancy is still predominant. The most common obstetric complication was preterm delivery. The most common cardiac complication was congestive heart failure, comparing to our data and results 8 patients (30.8%) had SVT, 8 patients (30.8%) have hypertension accompanying the cardiac disease, 3 patients (11.5%) with pulmonary hypertension, 3 patients (11.5%) complicated by cardiomyopathy, 2 patients (7.7%) complicated by heart failure, 2 patients (7.7%) complicated by ventricular fibrillation, and just only one patient (3.8%) complicated by pulmonary embolism, there is a strong statistically significant link between cardiac disease and occurrence of medical complication during the pregnancy and delivery as well as there is a strong correlation between cardiac disease and obstetric complication. In term of 22 patients (84.6%) delivered by caesarean section, 8 patients (30.8%) having hypertension during the pregnancy, 7 patients (26.9%) delivered preterm, 2 patients (7.7%) delivered died baby (IUFD), and 6 patients (23.1%) have history of miscarriage recurrent. In Kristina Kernell<sup>110</sup>.. In women with CHD, these characteristics were repeated in their firstborn children. No increased risks were found in children of men with CHD or in children of women with Marfan syndrome. There was no increased risk of aortic dissection in women with Marfan syndrome during pregnancy compared to women with Marfan syndrome who did not give birth. Higher frequencies of cardiac arrhythmia and valvular heart disease were found after childbirth in women with Marfan syndrome. Pregnancy in women with CHD is a high-risk situation associated with increased risk of adverse neonatal outcomes for the expected child. Pregnancy in women without CHD, but where the father has CHD is not so associated with increased risk of adverse obstetric or neonatal outcomes. Pregnancy in women with Marfan syndrome is not associated with adverse outcomes for the expected child. In our study with respect to fetal outcomes we didn't included the father history of CHD, and results appeared as follows 4 babies (15.4%) delivered have congenital heart disease, 7 babies (26.9%) premature, 5 babies (19.2) with IUGR, one baby (3.8%) stillbirth, and one baby (3.8%) died neonate. Statistically significant, there is a strong correlation between maternal cardiac disease and neonatal complications.<sup>(111)</sup>

## CONCLUSION

Cardiac disease is associated with significant maternal and neonatal morbidity and mortality among pregnant women. Women of childbearing age who are at risk for or have cardiovascular disease should receive counseling and treatment from a multidisciplinary team that includes a gynecologist and a cardiologist if they need cardiothoracic surgery. Limitation: The limitation of this study is partially due to the small size of the sample and being confined to only one hospital, which underestimates the actual burden of the problem.

## Recommendations

After conducting our study, we would like to recommend future studies done health care should be given awareness women about pregnancy various adaption which are not

always tolerated by patient with existing heart disease. Health care must incorporate intervention that educate women about pre pregnancy counselling and antenatal fowl up with multidisciplinary team to improve pregnancy and neonatal outcome. Healthcare organizations should also make efforts in making maternal and antenatal care more easily accessible and economical so that all women from low socioeconomic statuses can take advantage of it. These efforts and interventions will help societies combat adverse effects of pregnancy in their respective localities.

## REFERENCES

1. Cardiac disease in pregnancy multicentric study of pregnancy outcome in woman with heart disease.
2. Uri ELKAYAM,MD,sored gland 2001 md,petronella G.pieper ,MD high risk cardiac disease in pregnancy
3. De swiet m and nelson-pierey (2004) cardiac disease in confidential, Enquiren in to maternal and child health. why mother dia, 2000,2002
4. Baumgrtner H,Bonhoeffer p,DE Groet nm ,de haan f , dear field JE , etal. Tark force on the management of grown-up congenital heart disease of the European society of cardiology (ESC). ESC guidelines. Eur heart J. 2010,31:2915-2957
5. Elkayam u, Gleicher n. hemodynamic and cardiac function during normal pregnancy ang the puerperium. In: Elkaism u, gleichern editors, cardiac problem in pregnancy. 3rd edition new York,ny:wiky liss, 1998:3-20
6. Ouzounian JG, Elkayam u. physiologic changes during normal pregnancy and delivery, cadiol uin 2012:30 :317-20
7. Elkayam u, soral g, petronella G, Candice k. high-risk cardiac disease in pregnancy. Journal of American colleged of cardiology 2016:68:396-410
8. Ashrafi R, Curtis SL. Heart Disease and Pregnancy. Cardiol Ther. 2017 Dec;6(2):157-173. [PMC free article] [PubMed]
9. European Society of Gynecology (ESG). Association for European Paediatric Cardiology (AEPC). German Society for Gender Medicine (DGesGM). Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L., ESC Committee for Practice Guidelines. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011 Dec;32(24):3147-97. [PubMed]
10. Pregnancy complicated by maternal heart disease at the National Maternity Hospital, Dublin, Ireland, 1969 to 1978
11. 11 McFaul PB, Dornan JC, Lamki H, et al. Pregnancy complicated by maternal heart disease. A review of 519 women. Br J Ostet Gynaecol. 1988; 95: 861-7
12. Pregnancy Mortality Surveillance System.[https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-mortality-surveillance-system.htm?CDC\\_AA\\_refVal=https%3A%2F%2Fwww.cdc.gov%2Freproductivehealth%2Fmaternalinfanthealth%2Fpmss.html](https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-mortality-surveillance-system.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Freproductivehealth%2Fmaternalinfanthealth%2Fpmss.html). Accessed September 29, 2019.Google Scholar
13. Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives:

- Reviewing Maternal Deaths to Make Motherhood Safer 2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH; 2007
14. Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Why Mothers Die 2000–2002. The Sixth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH; 2004
  15. Copyright © 2018 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.
  16. 16 Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2019. For permissions, please email: journals.permissions@oup.com
  17. B.M. Weiss, L.K. von Segesser, E. Alon, et al. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984–1996 *Am J Obstet Gynecol*, 179 (1998), pp. 1643–1653 Article Download PDF View Record in Scopus Google Scholar
  18. Sakshi Arora Hans 13th Edition updated from William's obstetrics 25/e [www.jaypeebrothers.com](http://www.jaypeebrothers.com)
  19. Hunter S, Robson SC . Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992; 68:540–3. doi:10.1136/hrt.68.12.540. pmid:<http://www.ncbi.nlm.nih.gov/pubmed/1467047> FREE Full Text Google Scholar
  20. Robson SC , Dunlop W , Moore M , et al . Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. *Br J Obstet Gynaecol* 1987; 94:1014– 27. doi:10.1111/j.1471-0528.1987.tb02285.x pmid:<http://www.ncbi.nlm.nih.gov/pubmed/3322366> CrossRef PubMed Web of Science Google Scholar
  21. Robson SC, Hunter S, Boys RJ, et al . Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989;256:H1060–5. doi:10.1152/ajpheart.1989.256.4 .H1060 pmid:<http://www.ncbi.nlm.nih.gov/pubmed/2705548> PubMed Web of Science Google Scholar
  22. Melchiorre K, Sharma R, Thilaganathan B. Cardiac structure and function in normal pregnancy. *Curr Opin Obstet Gynecol* 2012;24:413–1. doi:10.1097/GCO.0b013e328359826f pmid:<http://www.ncbi.nlm.nih.gov/pubmed/23000697> CrossRef PubMed Google Scholar
  23. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. *Semin Perinatol* 2015;39:512–9. doi:10.1053/j.semperi.2015.08.003 pmid:<http://www.ncbi.nlm.nih.gov/pubmed/26452316> CrossRef PubMed Google Scholar
  24. Sciscione AC, Ivester T, Largoza M, Manley J, Shlossman P, Colmorgen GH. Acute pulmonary edema in pregnancy. *Obstet Gynecol*. 2003 Mar;101(3):511-5. [PubMed: 12636955]
  25. McFaul PB, Dornan JC, Lamki H, Boyle D. Pregnancy complicated by maternal heart disease. A review of 519 women. *Br J Obstet Gynaecol*. 1988 Sep;95(9):861-7. [PubMed: 3191059]
  26. Selzer A. Risks of pregnancy in women with cardiac disease. *JAMA*. 1977 Aug 22;238(8):892-3. [PubMed: 577983]
  27. Sanghavi M., J.D. Rutherford Cardiovascular physiology of pregnancy *Circulation*, 130 (2014), pp. 1003–1008 View Record in Scopus Google Scholar
  28. Elkayam U., N. Gleicher Hemodynamics and cardiac function during normal pregnancy and the puerperium. *Cardiac problems in pregnancy* (3rd ed.), Wiley-Liss, New York, NY (1998), pp. 3–20 Google Scholar
  29. Jepson J.H. Endocrine control of maternal and fetal erythropoiesis *Can Med Assoc J*, 98 (1968), pp. 844–847 View Record in Scopus Google Scholar
  30. Mahendru A.A., T.R. Everett, I.B. Wilkinson, et al. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens*, 32 (2014), pp. 849–856 View Record in Scopus Google Scholar
  31. Jones C.M., F.C. Greiss The effect of labor on maternal and fetal circulating catecholamines *Am J Obstet Gynecol*, 144 (1982), pp. 149–153 Article Download PDF View Record in Scopus Google Scholar
  32. Valensise H, Novelli GP, Vasapollo B, Borzi M, Arduini D, Galante A, Romanini C. Maternal cardiac systolic and diastolic function: relationship with uteroplacental resistances. A Doppler and echocardiographic longitudinal study. *Ultrasound Obstet Gynecol*. 2000 Jun;15(6):487-97. [PubMed: 11005116]
  33. Pandey AK, Banerjee AK, Das A, Bhawani G, Kumar A, Majumadar B, Bhattacharya AK. Evaluation of maternal myocardial performance during normal pregnancy and post-partum. *Indian Heart J*. 2010 Jan-Feb;62(1):64-7. [PubMed: 21180037]
  34. Estensen ME, Beitnes JO, Grindheim G, Aaberge L, Smiseth OA, Henriksen T, Aakhus S. Altered maternal left ventricular contractility and function during normal pregnancy. *Ultrasound Obstet Gynecol*. 2013 Jun;41(6):659-66. [PubMed:23001841]
  35. Morales A, Painter T, Li R, Siegfried JD, Li D, Norton N, Hersherberger RE. Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. *Circulation*. 2010 May 25;121(20):2176-82. [PMC free article: PMC2900861] [PubMed:20458009]
  36. Arany Z, Foo SY, Ma Y, Ruas JL, Bommi-Reddy A, Girmun G, Cooper M, Laznik D, Chinsomboon J, Rangwala SM, Baek KH, Rosenzweig A, Spiegelman BM. HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1 $\alpha$ . *Nature*. 2008 Feb 21;451(7181):1008-12. [PubMed: 18288196]
  37. Chapman AB Abraham wt, zamudio S, Caffeine, Merouani A, young D, Johnson A, Osiris F, Goldberg C, Moore LG, Dahl's T, schist Rwanda. temporal relationships between hormonal and hemodynamics changes in early human pregnancy. *kidney isn't in 1998: dec*, 54(6) 2056- 63(pubmed9853271)
  38. Tanous D., S.C. Siu, J. Mason, et al. B-type natriuretic peptide in pregnant women with heart disease *J Am Coll Cardiol*, 56 (2010), pp. 1247–1253 Article Download PDF View Record in Scopus Google Scholar
  39. Regitz-Zagrosek V., C. Blomstrom Lundqvist, C. Borghi, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy *Eur Heart J*, 32 (2011), pp. 3147–3197 View Record in Scopus Google Scholar
  40. Robson S.C., S. Hunter, M. Moore, et al. Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. *Br J Obstet Gynaecol*, 94 (1987), pp. 1028–1039
  41. Campos, J.L. Andrade, J. Bocanegra, et al. Physiologic multivalvular regurgitation during pregnancy: a longitudinal Doppler echocardiographic study *Int J Cardiol*,



- 40 (1993), pp. 265-272 Article Download PDF View Record in Scopus Google Scholar
42. Kanal E., A.J. Barkovich, C. Bell, et al. ACR guidance document for safe MR practices: 2007 AJR Am J Roentgenol, 188 (2007), pp. 1447- 1474 View Record in Scopus Google Scholar
43. Regitz-Zagrosek, V., C.blomstorm lundqvist, c. borghi, et al. ESC guidelines on mangment of cardiovascular diseases during pregnancy eur heart J, 32(2011), pp.3147-3197 View record in scopus google schola.
44. Siu S.C., M. Sermer, J.M. Colman, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease Circulation, 104 (2001), pp. 515-521 CrossRef View Record in Scopus Google Scholar
45. Celermajer DS. Atrial septal defects: even simple congenital heart diseases can be complicated. Eur Heart J. 2018 Mar 21;39(12):999-1001. [PubMed]
46. Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. J Am Coll Cardiol 2007; 49: 2303–2311. [PubMed] [Google Scholar]
47. Yentis SM, Steer PJ, Plaat F. Eisenmenger's syndrome in pregnancy: maternal and fetal mortality in the 1990s. Br J Obstet Gynaecol. 1998;105(8):921–922. [PubMed] [Google Scholar]
48. Veldtman GR, Connolly HM, Grogan M, Ammash NM, Warnes CA. Outcomes of pregnancy in women with tetralogy of Fallot. J Am Coll Cardiol. 2004;44(1):174–180. [PubMed] [Google Scholar]
49. Gelson E, Gatzoulis M, Steer PJ, Lupton M, Johnson M. Tetralogy of Fallot: maternal and neonatal outcomes. BJOG. 2008;115(3):398–402. [PubMed] [Google Scholar]
50. Elkayam U., S. Goland, P.G. Pieper, et al. High-risk cardiac disease in pregnancy, Part I J Am Coll Cardiol, 68 (2016), pp. 396-410 Article Download PDF View Record in Scopus Google Scholar
51. Silversides C.K., J.M. Colman, M. Sermer, et al. Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis Am J Cardiol, 91 (2003), pp. 1386-1389. Article Download PDF View Record in Scopus Google Scholar
52. Silversides C.K., J.M. Colman, M. Sermer, et al. Cardiac risk in pregnant women with rheumatic mitral stenosis Am J Cardiol, 91 (2003), pp. 1382-1385. Article Download PDF View Record in Scopus Google Scholar
53. Oylumlu M., K. Aykent, H.E. Soydinc, et al. Pulmonary balloon valvuloplasty during pregnancy Case Rep Cardiol, 2012 (2012), p. 353168 View Record in Scopus Google Scholar
54. Drenthen W., P.G. Pieper, J.W. Roos-Hesselink, et al. Non-cardiac complications during pregnancy in women with isolated congenital pulmonary valvar stenosis Heart, 92 (2006), pp. 1838-1843 CrossRef View Record in Scopus Google Scholar
55. Drenthen W., P.G. Pieper, M. Ploeg, et al. Risk of complications during pregnancy after Senning or Mustard (atrial) repair of complete transposition of the great arteries Eur Heart J, 26 (2005), pp. 2588-2595 CrossRef View Record in Scopus Google Scholar
56. Elkayam U., F. Bitar Valvular heart disease and pregnancy: Part II: prosthetic valves J Am Coll Cardiol, 46 (2005), pp. 403-410 Article Download PDF View Record in Scopus Google Scholar
57. Monteiro A.V., J. Rebelo, L. Patricio, et al. Ten years' experience of pregnancy outcomes in women with cardiac valvulopathies: are valve prostheses worst? J Heart Valve Dis, 24 (2015), pp. 368-375 View Record in Scopus Google Scholar
58. Van Hagen I.M., J.W. Roos-Hesselink, T.P. Ruys, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC) Circulation, 132 (2015), pp. 132-142 View Record in Scopus Google Scholar
59. Avila W.S., E.G. Rossi, M. Grinberg, et al. Influence of pregnancy after bioprosthetic valve replacement in young women: a prospective five- year study J Heart Valve Dis, 11 (2002), pp. 864-869 View Record in Scopus Google Scholar
60. Van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of cardiology registry of pregnancy and cardiac disease (ROPAC). Circulation 2015; 132:132–42. doi:10.1161/circulationaha.115.015242 pmid: http://www.ncbi.nlm.nih.gov/pubmed/26100109 Abstract/FREE Full Text Google Scholar
61. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017; 38:2739–91. doi:10.1093/ eurheartj/ chx391pmid:http://www.ncbi.nlm.nih.gov/pubmed/288866 19 CrossRef PubMed Google Scholar
62. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary: a report of the American College of Cardiology/American heart association Task force on practice guidelines. J Am Coll Cardiol 2014; 63:2438–88.doi: 10.1016/j.jacc.2 014.02.537 pmid: http://www.ncbi.nlm.nih.gov/pubmed/24603192 FREE Full Text Google Scholar
63. Silversides C.K., J.M. Colman, M. Sermer, et al. Cardiac risk in pregnant women with rheumatic mitral stenosis Am J Cardiol, 91 (2003), pp. 1382-1385. Article Download PDF View Record in Scopus Google Scholar
64. Avila W.S., M. Grinberg, L. Decourt, et al. Evolução clínica de portadoras de estenose mitral no ciclo gravídico-puerperal Arq Bras Cardiol, 58 (1992), pp. 359-364 View Record in Scopus Google Scholar
65. Roos-Hesselink J.W., T.P. Ruys, J.I. Stein, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology Eur Heart J, 34 (2013), pp. 657-665 CrossRef View Record in Scopus Google Scholar
66. Drenthen W., P.G. Pieper, J.W. Roos-Hesselink, et al. Pregnancy and delivery in women after Fontan palliation Heart, 92 (2006), pp. 1290-1294 CrossRef View Record in Scopus Google Scholar
67. Gouton M., J. Nizard, M. Patel, et al. Maternal and fetal outcomes of pregnancy with Fontan circulation: a multicentric observational study Int J Cardiol, 187 (2015), pp. 84-89 Article Download PDF View Record in Scopus Google Scholar
68. Kowalik E., A. Klisiewicz, E.K. Biernacka, et al. Pregnancy and long-term cardiovascular outcomes in women with congenitally corrected transposition of the great arteries Int J Gynaecol Obstet, 125 (2014), pp. 154-157 Article Download PDF CrossRef View Record in Scopus Google Scholar
69. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the registry of pregnancy and cardiac disease (ROPAC) of the European Society of cardiology. Eur J Heart Fail

- 2016;18:1119–28.doi:10.1002/ejhf.594  
 pmid:http://www.ncbi.nlm.nih.gov/pubmed/27384461  
 Cross Ref PubMed Google Scholar
70. Bédard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* 2009;30:256–65.doi: 10.1093/eurheartj/ehn597 pmid:http://www.ncbi.nlm.nih.gov/pubmed/19147605 CrossRef PubMed Web of Science Google Scholar
71. Bédard E., K. Dimopoulos, M.A. Gatzoulis Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J*, 30 (2009), pp. 256-265 View Record in Scopus Google Scholar
72. Galie N., M. Humbert, J.L. Vachiery, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension *Eur Heart J*, 37 (2016), pp. 67-119 CrossRef View Record in Scopus Google Scholar
73. Jaïs X., K.M. Olsson, J.A. Barbera, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era *Eur Respir J*, 40 (2012), pp. 881-885 CrossRef View Record in Scopus Google Scholar
74. Sliwa K., D. Hilfiker-Kleiner, M.C. Petrie, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy *Eur J Heart Fail*, 12 (2010), pp. 767-778 CrossRef View Record in Scopus Google Scholar
75. Elkayam U., S. Goland, P.G. Pieper, et al. High-risk cardiac disease in pregnancy: Part II *J Am Coll Cardiol* (2016), pp. 502-516 Article Download PDF View Record in Scopus Google Scholar
76. Sliwa K., A. Mebazaa, D. Hilfiker-Kleiner, et al. Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM *Eur J Heart Fail*, 19 (2017), pp. 1131-1141 CrossRef View Record in Scopus Google Scholar
77. Hilfiker-Kleiner D., K. Sliwa Pathophysiology and epidemiology of peripartum cardiomyopathy *Nat Rev Cardiol*, 11 (2014), pp. 364-370 CrossRef View Record in Scopus Google Scholar
78. Halkein J., S.P. Tabruyn, M. Ricke-Hoch, et al. MicroRNA-146a is a therapeutic target and biomarker for peripartum cardiomyopathy *J Clin Invest*, 123 (2013), pp. 2143-2154 CrossRef View Record in Scopus Google Scholar
79. Sliwa K., J. Fett, U. Elkayam Peripartum cardiomyopathy *Lancet*, 368 (2006), pp. 687-693 Article Download PDF View Record in Scopus Google Scholar
80. Goland S., F. Bitar, K. Modi, et al. Evaluation of the clinical relevance of baseline left ventricular ejection fraction as a predictor of recovery or persistence of severe dysfunction in women in the United States with peripartum cardiomyopathy *J Card Fail*, 17 (2011), pp. 426-430 Article Download PDF View Record in Scopus Google Scholar
81. Elkayam U. Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy *J Am Coll Cardiol*, 64 (2014), pp. 1629-1636 Article Download PDF View Record in Scopus Google Scholar
82. Avila W.S., M.E.C. Carvalho, C.K. Tschäen, et al. Gravidez em portadoras de cardiomiopatia periparto. Estudo prospectivo e comparativo *Arq Bras Cardiol*, 79 (2002), pp. 484-488 View Record in Scopus Google Scholar
83. Sliwa K., L. Blauwet, K. Tibazarwa, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof- of-concept pilot study *Circulation*, 121 (2010), pp. 1465-1473 View Record in Scopus Google Scholar
84. Haghikia A., E. Podewski, E. Libhaber Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy *Basic Res Cardiol*, 108 (2013), p. 366 View Record in Scopus Google Scholar
85. Fett J.D. Caution in the use of bromocriptine in peripartum cardiomyopathy *J Am Coll Cardiol*, 51 (2008), p. 2083 Article Download PDF View Record in Scopus.
86. Elkayam U., S. Jalnapurkar, M. Barakat Peripartum cardiomyopathy *Cardiol Clin*, 30 (2012), pp. 435-440 Article Download PDF View Record in Scopus Google Scholar
87. Duncker D., A. Haghikia, T. König, et al. Risk for ventricular fibrillation in peripartum cardiomyopathy with severely reduced left ventricular function: value of the wearable cardioverter/defibrillator *Eur J Heart Fail*, 16 (2014), pp. 1331-1336 CrossRef View Record in Scopus Google Scholar
88. Yentis SM, Steer PJ, Plaat F. Eisenmenger's syndrome in pregnancy: maternal and fetal mortality in the 1990s. *Br J Obstet Gynaecol.* 1998;105(8):921–922. [PubMed] [Google Scholar]
89. Bossiter JP, Repke JT, Morales AJ, et al. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995;173:1599–606.doi:10.1016/0002-9378(95) 90655-X pmid:http://www.ncbi.nlm.nih.gov/pubmed/7503207 CrossRef PubMed Web of Science Google Scholar
90. Meijboom LJ, Vos FE, Timmermans J, et al. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J* 2005;26:914–20. doi:10.1093/eurheartj/ehi103pmid:http://www.ncbi.nlm.nih.gov/pubmed/15681576 CrossRef PubMed Web of Science Google Scholar
91. Donnelly RT, Pinto NM, Kocolas I, et al. The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. *J Am Coll Cardiol* 2012; 60:224–9. doi: 10.1016/j.jacc.2012.03.051 pmid:http://www.ncbi.nlm.nih.gov/pubmed/22789886 FREE Full Text Google Scholar
92. Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati international Turner syndrome meeting. *Eur J Endocrinol* 2017;177:G1–70.doi:10.1530/EJE-17-0430 pmid:http://www.ncbi.nlm.nih.gov/pubmed/28705803 Abstract/FREE Full Text Google Scholar
93. Steer PJ, Gatzoulis MA, Baker P., Heart Disease and Pregnancy, 2006 London RCOG Press Google Scholar Google Preview WorldCat COPAC
94. Nelson-Piercy C. Nelson-Piercy C. Heart disease, Handbook of Obstetric Medicine, 2002<sup>nd</sup> Edn Martin Dunitz Taylor & Francis Group Google Scholar Google Preview WorldCat COPAC
95. Boyle RK. Anaesthesia in parturients with heart disease: a five-year review in an Australian tertiary hospital, *Int J Obstet Anesth*, 2003, vol. 12 (pg. 173-7) Google Scholar CrossRef PubMed WorldCat

96. Tamhane P, O'sullivan G, Reynolds F. Oxytocin in parturients with cardiac disease, *Int J Obstet Anesth*, 2006, vol. 15 (pg. 332-3) Google ScholarCrossrefPubM
97. Sakshi Arora Hans 13th Edition updated from William's obstetrics 25/e [www.jaypeebrothers.com](http://www.jaypeebrothers.com)
98. High Burden of Cardiac Disease in Pregnancy at a National Referral Hospital in Western Kenya Rebecca Lumsden, MD, Felix Barasa, MBChB, MMed, Lawrence P. Park, Ph.D, Christian B. Ochieng, MSc, Joy M. Alera, BS, Heather C. Millar, MD, Gerald S. Bloomfield, MD, and Astrid Christoffersen- Deb, MDCM, *Dphi*. v.15(1); 2020
99. Parity and risk of maternal cardiovascular disease: A dose-response meta-analysis of cohort studies Wenzhen Li, Wenyu Ruan, Zuxun Lu, Dongming Wang. 1 April 2019
100. Cardiac Complications during Pregnancy Related to Parity in Women with Congenital Heart Disease Eva Furenäs, Peter Eriksson, Ulla-Britt Wennerholm, and Mikael Dellborg. 2020.
101. The correlation between maternal age, parity, cardiac diastolic function and occurrence rate of pre-eclampsia Dan Zhu, Weiyu Chen, Yuchen Pan, Tingcui Li, Ming Cui & Baoxia Chen. 23 April 2021
102. Is a planned caesarean section in women with cardiac disease beneficial? Titia P E Ruys, Jolien W Roos-Hesselink, Antonia Pijuan-Domènech, Elena Vasario, Ilshat R Gaisin, Bernard Lung, Leisa J Freeman, Elaine P Gordon, Petronella G Pieper, Roger Hall, Eric Boersma, Mark R Johnson, ROPAC investigators. 2014 Dec 24.
103. Is vaginal delivery or caesarean section the safer mode of delivery in patients with adult congenital heart disease? Victoria Asfour, Michael O. Murphy, Rizwan Attia. 10 April 2013.
104. Cardiac disease in pregnancy CY Li, JE Sanderson. 4 December 1997 105 Cardiac disease in pregnancy Surabhi Nanda, Catherine Nelson-Piercy, Lucy Mackillop. 2012 Dec.
105. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. *Circulation*. 2006;113(4):517- 524. doi:10.1161/ circulationaha.105.589655
106. Yaghoubi A, Pezeshkian M, Imani S, Alizadeye Asl A. Analysis of Maternal-Fetal outcomes of Valvular Heart Surgeries in Pregnant Women. *Zahedan Journal of Research in Medical Sciences*. 2009;12(1):40-43
107. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril*. 2003;79(3):577-584
108. Tateno S, Niwa K, Nakazawa M, Akagi T, Shinohara T, Yasuda T. Arrhythmia and conduction disturbances in patients with congenital heart disease during pregnancy: multicenter study. *Circ J*. 2003;67(12):992-997.
109. Pregnancy complications in women with heart disease. Thida Thanajiraprapa & Vorapong Phupong. 11 Nov 2009.
110. Cardiac disease in pregnancy and consequences for reproductive outcomes, comorbidity and survival Kristina Kernell.

\*\*\*\*\*