

Cardiomyopathies and Congenital Heart Disease in Pregnancy

Kardiomyopathien und kongenitale Vitia in der Schwangerschaft



Authors

Mechthild Westhoff-Bleck¹, Denise Hilfiker-Kleiner¹, Sabine Pankuweit², Bernhard Schieffer²

Affiliations

- 1 Medizinische Hochschule Hannover, Molekulare Kardiologie, Abteilung für Kardiologie und Angiologie, Hannover, Germany
- 2 Klinik für Innere Medizin, Kardiologie, Angiologie und internistische Intensivmedizin, Klinikum der Philipps-Universität, Marburg, Germany

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Correspondence

Prof. Dr. Bernhard Schieffer
Klinik für Innere Medizin, Kardiologie, Angiologie
und internistische Intensivmedizin,
Klinikum der Philipps-Universität, Marburg
Baldingerstraße, 35043 Marburg, Germany
Bernhard.schieffer@staff.uni-marburg.de

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ABSTRACT

Pregnancy-associated diseases of the cardiovascular system occur in up to 10% of all pregnancies and the incidence is increasing. Besides congenital heart disease or pre-existing cardiomyopathy in the mother, the clinical focus has moved especially to peripartum cardiomyopathy (PPCM) because of the condition's dramatic clinical course and the identification

of the underlying mechanisms. This review article concentrates therefore on PPCM, which occurs either in the last month of pregnancy or in the first 6 months following delivery in women with previously healthy hearts. The global incidence is estimated today at roughly 1 : 1000 pregnancies. The condition is heterogeneous, ranging from mild disease to severe acute heart failure with cardiogenic shock and sudden cardiac death of the mother. Important risk factors are pregnancy-associated hypertensive complications, multiple pregnancy and greater maternal age. The pathogenesis comprises cleavage, induced by increased oxidative stress, of the lactation hormone prolactin into a toxic hormone fragment that damages blood vessels, known as the 16-kDalton protein fragment. The lactation-blocking drug bromocriptine prevents prolactin release and promotes healing of PPCM in combination with pharmacological heart failure therapy; it appears to prevent recurrence in subsequent pregnancies. Uncomplicated pregnancy is possible in most patients with congenital heart disease. The foetal complications include an increased abortion rate, prematurity and smallness for gestational age, as well as an increased risk of cardiac malformations. The maternal risk comprises mainly arrhythmias, progressive heart failure and thromboembolic complications, with the risk of vessel dissection with a low mortality risk of < 1% in the case of aortopathies. Individual risk assessment and corresponding close monitoring of the pregnancy are required.

ZUSAMMENFASSUNG

Schwangerschaftsassozierte Erkrankungen des kardiovaskulären Systems treten bei bis zu 10% aller Schwangerschaften mit zunehmender Inzidenz auf. Aufgrund der klinischen Dramatik des Erkrankungsverlaufes und der Identifizierung zugrunde liegender Mechanismen ist neben angeborenen Herzfehlern oder vorbestehenden Kardiomyopathien der Mutter insbesondere die peripartale Kardiomyopathie (PPCM) in den klinischen Fokus gerückt. Diese Übersichtsarbeit konzentriert sich deshalb auf das Krankheitsbild der PPCM, die entweder im letzten Monat der Schwangerschaft oder in den ersten 6 Monaten nach einer Entbindung bei zuvor herzgesunden Frauen auftritt. Die weltweite Inzidenz wird heute auf ca. 1 : 1000 Schwangerschaften geschätzt. Das Krankheitsbild ist heterogen mit milden Verläufen bis hin zu schwerer akuter Herzinsuffizienz mit kardiogenem Schock und plötzlichem

Herztod der Mutter. Wichtige Risikofaktoren sind schwangerschaftsassozierte hypertensive Komplikationen, Mehrlingschwangerschaften und höheres Alter der Mütter. Die Pathogenese beinhaltet eine durch vermehrten oxidativen Stress induzierte Spaltung des Stillhormons Prolaktin in ein blutgefäßschädigendes toxisches Hormonfragment (das sog. 16-kDa-Protein-Fragment). Bromocriptin, als Abstillmedikament, verhindert die Freisetzung des Prolaktins und fördert in Kombination mit einer medikamentösen Herzinsuffizienztherapie die Heilung der PPCM und scheint Rezidive bei Folgeschwangerschaften zu verhindern. Bei den meisten Patientinnen mit

angeborenen Herzfehlern sind Schwangerschaften komplikationslos möglich. Zu den fetalen Komplikationen gehören neben einer erhöhten Abortrate, Früh- und Mangelgeburtslichkeit ein erhöhtes Risiko kardialer Fehlbildungen. Das mütterliche Risiko umfasst hauptsächlich Rhythmusstörungen, eine progrediente Herzinsuffizienz, thrombembolische Komplikationen und bei Aortopathien das Risiko von Gefäßdissektionen mit einem geringen Mortalitätsrisiko von < 1%. Erforderlich ist eine individuelle Risikoabschätzung und entsprechende engmaschige Betreuung in der Schwangerschaft.

Introduction

Cardiomyopathies are defined, according to a position paper of the European Society of Cardiology, as myocardial diseases characterised by structural or functional restrictions of the myocardium in the absence of coronary heart disease, hypertension, valvular disease or congenital cardiac disease that could explain the dysfunction [1]. Based on their specific morphological and functional phenotypes, the cardiomyopathies are divided into hypertrophic, dilated, arrhythmogenic and restrictive forms, which are readily identifiable in clinical practice by diagnostic echocardiography. Every form or entity can be due to a familial form because of a potentially identifiable and often monogenetic change, or can have other non-familial and non-genetic causes.

Dilated cardiomyopathy is characterised by dilation of the left ventricle with concomitant impairment of function, and a familial form, usually due to autosomal dominant mutations in genes of proteins of the cytoskeleton, the sarcomere, the nuclear membrane or the intercalated discs, can be found in approximately 25% of all patients. Non-familial forms can be caused by malnutrition or by infectious, autoimmune or toxic causes (alcohol and chemotherapeutic agents).

In 2008, pregnancy or peripartum cardiomyopathy (PPCM) was classified by Elliot et al. as a separate idiopathic, non-familial and non-genetic cardiomyopathy. It is therefore a cardiomyopathy that is characterised by left ventricular systolic dysfunction (<45%), which occurs at the end of pregnancy or in the months following delivery [2, 3]. Left ventricular dilation can but does not have to be detectable at the same time, but other causes of cardiac dysfunction must be excluded and there must be a temporal association with pregnancy. Diagnosis of peripartum cardiomyopathy is therefore a diagnosis of exclusion.

Due to advances in the treatment of congenital heart defects, a large number of women reach child-bearing age even with complex congenital heart defects. Congenital heart disease now represents the largest number of pregnant women with structural heart disease accounting for over 60–80% [4]. Congenital heart diseases are a non-homogeneous group that includes simple defects with a low pregnancy-associated risk and complex lesions with a significant complication rate [4–11]. The foetal complications include an increased abortion rate, prematurity and smallness for gestational age, as well as an increased risk of cardiac mal-

formations. Depending on the underlying disease, the cardiac malformation risk is between 2.5 and up to 50%.

The maternal risk comprises mainly arrhythmias, progressive heart failure and thrombembolic complications, with the risk of vessel dissection in the case of aortopathies. Cohort studies report a low mortality risk of < 1% [9]. However, only a small percentage of high-risk patients were included so the risks of pregnancy and delivery may be underestimated particularly in these patients.

Peripartum Cardiomyopathy (PPCM)

Pregnancy-associated diseases of the cardiovascular system affect up to 10% of all pregnancies and the incidence is increasing. The increasing obesity in the population, greater maternal age and increased multiple pregnancies appear to be promoting this trend. Besides bleeding complications, cardiomyopathies in pregnancy and in the peripartum period are today still among the most frequent causes of peripartum morbidity and mortality. Peripartum cardiomyopathy (PPCM), heart failure that can occur both acutely and gradually shortly before or after delivery, represents a high risk for sustained damage to the young mother's health, and may cause death [2, 12, 13].

Incidence

The incidence of PPCM is estimated globally at approximately 1:1000 pregnancies. There are no reliable figures in Germany but estimates assume a prevalence of 1:1500–2000 births [12]. PPCM is defined through a diagnosis of exclusion; in the position paper of the European Society of Cardiology from this year, which can be accessed at www.escardio.org [2], the definition states: "PPCM is an idiopathic cardiomyopathy that occurs in the last month of pregnancy or in the months following delivery or termination of pregnancy in women with previously healthy hearts". The only diagnostic criterion is the left ventricular ejection fraction (LVEF) measured by echocardiography or MRI, which should be $\leq 45\%$ [2]. Congenital or previously diagnosed heart disease such as chemotherapy-induced myocarditis, genetically caused cardiomyopathies or known dilated cardiomyopathies exclude PPCM.

Risk factors

To date, the aetiology of PPCM is largely unknown. However, a series of risk factors has been identified in the last few years. These include, for example, pregnancy-associated hypertensive diseases (pre-eclampsia, HELLP syndrome), which were found in nearly 50% of PPCM patients in Germany. Multiple pregnancy, multiparity and pregnancy at a later age, tocolysis and African and Afro-American origin also appear to be associated with an increased PPCM risk [12–14].

Diagnosis

Early diagnosis is essential for a good chance of cure. The diagnosis of PPCM is made more difficult by the fact that symptoms are often not clear and are sometimes difficult to distinguish from normal pregnancy symptoms such as oedema, shortness of breath and lethargy [2, 15]. The ECG is often normal also. Nonspecific chest symptoms, palpitations, nocturia and nausea or pulmonary oedema with orthopnoea and tachypnoea as part of cardiogenic shock, as well as restlessness and agitation are likewise possible. A delay in diagnosis and hence in the start of treatment contributes significantly to long-term morbidity and mortality. Moreover, spontaneous recovery is common in milder disease but the risk of recurrence with a severe disease course in a further pregnancy is markedly increased [12, 16, 17]. When making the diagnosis, it is important to measure biomarkers of cardiac damage/heart failure. Besides the recommended transthoracic echocardiography, laboratory measurement of natriuretic peptide (BNP or NT-proBNP) as soon as (pregnancy-associated) heart failure is suspected has proved to be a useful guide and should be measured early in a suspected case [18]. Measurement of troponin T (or troponin I) as well as determination of inflammatory markers (CRP, PCT, leucocyte count) helps to distinguish it from, for instance, myocarditis. Cardiac MRI should be performed in addition to follow-up echocardiography for differential diagnosis. A 12-channel ECG is also recommended for prompt detection of possible changes and an increased risk for ventricular arrhythmias.

Pathogenesis

The pathogenesis of PPCM is incompletely understood. It has been argued that it might be a vascular disease triggered by the hormonal milieu and oxidative stress in late pregnancy or the early post-delivery period. However, it remains unclear why only a small number of pregnant women develop any symptoms of PPCM at all. Based on the aetiology of dilated cardiomyopathy, inflammatory or genetic factors have also been postulated in the pathogenesis of PPCM, but analysis of cardiac muscle biopsies has yielded few indicative results. Only one genetic study in a study population of 172 patients with PPCM of mutations in proteins that are associated with dilated cardiomyopathy suggests a genetic predisposition in 15% of the patients, the majority of which involve changes in a structural protein named titin [15]. It can be assumed with certainty, however, that other exogenous and/or genetic factors are involved in the development of PPCM since patients with PPCM and changes in the titin gene develop the disease at an earlier time than patients with dilated cardiomyopathy and demonstrate normal left ventricular function again much more often subsequently. However, left ventricular func-

tion recovers in patients with PPCM in most cases, while mortality of 5–10% is described [16]. Infectious diseases, viral myocarditis, autoimmune phenomena or major blood loss at delivery are suggested as other possible causes [12–14].

Experimental studies showed that increased peripartum oxidative stress leads to cleavage of the lactation hormone prolactin into an N-terminal 16 kDa prolactin fragment (also called vasoinhibin), which then causes primary endogenous damage to the vascular system through vasotoxic, proinflammatory and proapoptotic effects [19]. The efficacy of bromocriptine, a blocker of prolactin secretion, was successfully tested as treatment in a mouse model of PPCM [19]. Since bromocriptine has long been used clinically as a drug to halt lactation, several attempts at treatment and a pilot study in South African patients followed, all of which showed very promising results [3]. A randomised multicentre dose-finding study initiated by us was sponsored by the BMBF and published last year [20]. This showed that, alongside basic heart failure treatment (beta-blockers, ACE inhibitors), a week of bromocriptine in a dosage of at least 2.5 mg p.o. and thrombosis prophylaxis sufficed to cure the majority of the patients and drastically reduce the high morbidity and mortality. This treatment concept was adopted in the current guidelines as the BOARD treatment regimen (Bromocriptine, Oral heart failure therapies, Anticoagulation, vasoRelaxing agents, and Diuretics) [21]. It is important that this treatment concept can only be used after delivery. In patients who become symptomatic in the last month of pregnancy, delivery should take place as soon as possible, and an interdisciplinary team of obstetricians, anaesthetists, cardiologists, cardiac surgeons and neonatologists should be on site. Following delivery, the BOARD regime should be started, depending on the patient's haemodynamic stability.

Treatment

With early diagnosis and treatment in accordance with guidelines, over 60% of patients recover completely within the first 12 months and a further 47% recover partially (i.e., improvement in left heart pump function [left ventricular ejection fraction, LV-EF] by at least 10% and at least one heart failure class [New York Heart Association, NYHA class]), and only about 3% remain in heart failure [20]. Even if these patients recover clinically and also echocardiographically, an increased long-term risk for sudden cardiac death unfortunately persists so that a defibrillator vest or possibly an implantable defibrillator (ICD) must be considered in high-risk patients even when cardiac function has recovered completely [22].

It is vitally important during intensive treatment that the frequently used stress hormones (adrenalin, dobutamine) are not used for intensive therapy as these can harm the patients and even cause irreversible terminal cardiac damage [23].

Further pregnancies

Further pregnancies are associated with a high risk of recurrence and patients should be counselled about this [16]. A subsequent pregnancy is not impossible, however, but patients must be monitored closely and delivery should take place in an experienced centre with the interdisciplinary collaboration of cardiology, anaesthesia, neonatology and gynaecology/obstetrics [17]. The

recommendations on medication for further planned pregnancy are in accordance with the guidelines [24]. It is important that ACE inhibitors are contraindicated during the first trimester because of their teratogenic effect; they are not a first-line treatment later in the pregnancy but can be used. The AT antagonists (angiotensin II type 1 receptor antagonists), mineralocorticoid receptor antagonists or ivabradine are contraindicated during pregnancy and lactation. Tapering and finally discontinuation of this medication are therefore necessary before the start of a further pregnancy. Beta-blockers may and should be continued during pregnancy (in Germany, only metoprolol is licensed during pregnancy). Diuretics should be used restrictively and only when clearly indicated (obvious fluid retention, pulmonary congestion); a pro-diabetogenic effect has been described for thiazide diuretics. The dosage should be adjusted because of their influence on placental perfusion and possible development of oligohydramnios. If an unplanned pregnancy occurs, the contraindicated drugs should be discontinued immediately as they can harm the embryo. An initial cardiology review with echocardiography, clinical examination and measurement of natriuretic peptides is recommended when pregnancy is diagnosed, at 4-week intervals from 20 weeks of gestation and at 2-week intervals after 30 weeks. In addition, close gynaecological and obstetric attendance is recommended for prompt detection of potential pregnancy complications. Close monitoring (echo, even weekly if necessary) is necessary in the last two months of pregnancy so that delivery can be initiated if there is clinical deterioration. The delivery should take place in an experienced centre with interdisciplinary collaboration between cardiology, gynaecology/obstetrics, anaesthesia and neonatology. Depending on the clinical status, LV-EF (left ventricular ejection fraction) and concomitant diseases, the delivery modality should also be considered (vaginal delivery versus section). Vaginal delivery is possible in stable patients, but elective caesarean section should be discussed with the patient if there are feared cardiological complications. Pharmacological inhibition of lactation by means of bromocriptine is recommended following delivery, with resumption of the oral heart failure medication, regardless of clinical symptoms and LVEF. Outpatient cardiological review following delivery is strongly recommended [25].

Long-term management

For the long-term management of PPCM patients, annual review is important, when medications can be checked and adjusted if necessary. Advice on family planning and contraception should be provided in every case. Hormone-free contraceptive methods (copper IUD, condoms) should be suggested, and a hormonal IUD containing levonorgestrel or an oral monopreparation containing desogestrel may be possible in women with heart failure. On the other hand, patients should be advised explicitly against oestrogen-containing preparations as there can be potentially negative interactions with the heart failure therapy and there is an increased thrombosis risk.

Congenital Heart Disease in Pregnancy

Antenatal care

Patients with congenital heart disease require individual counselling prior to pregnancy about the risks for mother and baby. This enables cardiac defects requiring treatment to be managed before pregnancy. The patient should be aware of high risks so that she can decide against pregnancy if appropriate. On the other hand, she must also be conscious of the medical consequences including the need for close monitoring during pregnancy.

With uncomplicated congenital heart defects, a single cardiology review to determine cardiac status often suffices, while all other patients should have one clinical review per trimester. Review of high-risk patients is necessary at intervals of 1–4 weeks from 18–20 weeks, depending on the risk profile and clinical picture as the haemodynamic stress increases. Organ screening ultrasound of the baby should be performed in all pregnant women at 20–24 weeks.

Pregnancies with significant cardiac risks, especially when high-risk, need referral to a maximum-care hospital with expertise in the treatment of congenital heart defects. Close interdisciplinary collaboration comprising joint cardiological and gynaecological care from the start is required.

Individual risk assessment is based on the underlying congenital condition, the cardiac lesions and clinical symptoms [9, 11, 24, 25]. When assessing the overall situation, the biomarker NT-proBNP can provide additional valuable information as NT-proBNP < 128 pg/ml in the 20th week of pregnancy was detected as an independent predictor of cardiac complications.

Prevention of complications

Patients with congenital heart disease have evidence of post-thrombotic syndrome in up to 60% of cases, necessitating the use of compression hose [26–28]. Iron deficiency anaemia should also be treated promptly (Hb < 11.5 g/dl).

Cardiac lesions such as severe aortic or mitral stenosis, native aortic isthmus stenosis and significant aneurysms of the aorta due to aortopathies should be treated interventional or surgically before a pregnancy.

Treatment of arterial hypertension is essential to reduce the risk of aortic complications; an average blood pressure of less than 120–130 mmHg is desirable and blood pressure peaks should be avoided. Beta-blocker therapy is regarded as basic treatment in Marfan syndrome.

Cardiac complications

The most frequent complications that occur include arrhythmias, progressive heart failure symptoms and thromboembolic complications.

Supraventricular tachycardias must be terminated as soon as possible as progressive heart failure symptoms with worsening of ventricular function are possible with sustained tachycardia. Depending on the existing status, prophylactic beta-blocker therapy and intermittent or long-term anticoagulation are required subsequently [24]. If there is no spontaneous conversion to sinus rhythm or haemodynamic instability is present, cardioversion is

indicated. Trans-oesophageal echocardiography is required to exclude intracardiac thrombus production with more prolonged supraventricular tachycardia. This necessitates an adequate fasting period because of the delayed gastric emptying during pregnancy.

Digitalis glycosides and adenosine can be used safely during pregnancy. The data are weak for specific antiarrhythmic agents (quinidine, procainide, flecainide, sotalol) but there are no known significant teratogenic risks. Use of amiodarone requires monitoring of thyroid function [11].

If heart failure symptoms occur, beta-blocker therapy is recommended initially. Treatment escalation with diuretics (hydrochlorothiazide, furosemide, spironolactone) is required if cardiac oedema or pulmonary congestion occurs. Even if foetal side effects are possible (bradycardia, reduced foetal growth), this medication should not be withheld from pregnant women when indicated but the foetal status should be monitored since improvement of the heart failure symptoms with optimisation of maternal haemodynamics improves foetal development and likelihood of survival. In the case of progressive heart failure, an interdisciplinary decision on how to proceed is necessary [15].

Thrombosis of a mechanical valve replacement is a life-threatening complication. There is currently no generally accepted concept of anticoagulation treatment during pregnancy [6]. Vitamin K antagonists (observing a maximum dose) and fractionated heparins are used, and close monitoring of the anti-Xa level is essential (target 0.6–1.2 IU/ml depending on valve type/risk factors) [6, 24]. In this case, anticoagulation is a balancing act between avoidance of thrombosis, bleeding complications and foetal malformation risks. The risk of valve thrombosis is higher on heparin therapy but the foetal malformation risk is lower. Hospital admission is essential if valve thrombosis occurs. Intravenous heparin therapy can be attempted initially (target PTT 60–80 s). If this is unsuccessful or the patient is haemodynamically unstable, lysis or surgical valve replacement is required.

Peripartum aortic dissection occurs in aortopathy or Marfan syndrome. Bicuspid aortic valves (increased risk with an aortic diameter > 50 mm) and Marfan syndrome (increased risk with aortic diameter > 45 mm) represent the most frequent congenital diseases associated with this complication. It should be noted that the risk of dissection is not limited to the delivery period only but is still markedly increased for a week post partum.

Fixed severe pulmonary hypertension due to Eisenmenger syndrome continues to be associated with high maternal morbidity and mortality. Medication with phosphodiesterase-5 inhibitors/prostacyclines is licensed as specific therapy. Management of these patients requires close interdisciplinary collaboration from the start. The haemodynamic stress is poorly tolerated even in the second trimester, which leads to reduced placental perfusion. Moreover, saturation of less than 90% is associated with a high early abortion rate.

If cardiac deterioration occurs, lung maturation should be initiated promptly and caesarean section should be planned.

Delivery

In most pregnancies, transvaginal delivery under epidural anaesthesia is possible, with a shortened second expulsive stage if appropriate. From the cardiological point of view, planning a primary section should be limited to high-risk patients. These are patients who are not able to deal with the up to 60% increase in cardiac output during labour or who have aortic aneurysms with a high dissection risk. The use of ECLS therapy should be considered early in the case of haemodynamic instability or severely impaired ventricular function.

Summary

PPCM is a life-threatening disease that occurs in women with previously healthy hearts. Since the symptoms cannot be clearly distinguished from other pregnancy-induced conditions or infectious diseases, cardiological investigation with echocardiography should always be performed in suspected cases. NT-proBNP is a suitable diagnostic marker, while classic cardiac enzymes do not allow indicative diagnosis of PPCM [12, 24]. Heart failure therapy in accordance with the guidelines should then be started as soon as possible [21]. Patients requiring intensive care or with a rapidly progressive disease course with cardiogenic shock should be transferred promptly to experienced centres that can provide extracorporeal life support (ECLS). Central bed allocation programmes such as IVENA, which is used in the German state of Hesse, can be utilised. At the University Hospital in Marburg, these patients receive interdisciplinary intensive care in the ECLS unit of the cardiology intensive care unit. Since PPCM has a very good recovery rate but is also associated with a sustained increased risk of recurrence, especially in subsequent pregnancies, and an increased risk of sudden cardiac death, PPCM should be followed by close cardiological follow-up and possibly defibrillator implantation.

Uncomplicated pregnancy is possible in most patients with congenital heart defects. Individual risk assessment is required, with corresponding close monitoring in pregnancy.

High-risk pregnancies require close interdisciplinary collaboration between gynaecologists and cardiologists. Patients should attend an expert centre even in early pregnancy. Pregnancies can be maintained longer by optimising the required cardiac treatment through close cardiological monitoring to detect increasing cardiac problems, or delivery can be planned before cardiac decompensation. When the mortality risk is high, delivery with ECLS available on standby can improve the prognosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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