Pregnancy and Heart Disease: Pregnancy-Associated Hypertension and Peripartum Cardiomyopathy

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Abstract: Cardiovascular diseases are major complications in pregnancy worldwide and the number of patients who develop cardiac problems during pregnancy is increasing. Pregnancy-associated hypertensive complications such as pre-eclampsia (PE) or peripartum cardiomyopathy (PPCM) are potentially life-threatening heart diseases emerging during pregnancy, under delivery or in the first postpartal months in previously healthy women. Both disease entities display substantial morbidity and mortality in the acute phase. Long-term effects are just beginning to be evaluated. Pathophysiologies are not clear but may to some degree overlap with regard to angiogenic imbalance and endothelial damage. Genetics, lifestyle, and comorbidities are important modulators of PE and PPCM. The present review summarizes the current knowledge on epidemiology and pathophysiology, provides information on diagnostic and prognostic biomarkers and highlights promising novel therapeutic approaches for PE and PPCM. (Curr Probl Cardiol 2018;43:364–388.)

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Introduction

Cardiovascular diseases (CVDs) are the most frequent cause of mortality globally. Although most of the patients suffering from CVDs are of older age, CVDs afflict also around 4% of all pregnancies in Western industrialized countries.[1]

CVDs complicating pregnancy consist of pre-existing cardiovascular pathologies (eg, congenital heart disease, genetic forms of cardiomyopathies, myocardial infarction, heart failure induced by myocarditis, and cardiotoxic treatment) or pregnancy-induced or associated CVDs, for example, pregnancy-associated hypertension (PAH), thrombotic complications (myocardial infarction, stroke, lung embolism), and peripartum cardiomyopathy (PPCM).[2,3] In the present review, we will focus mainly on PAH and on PPCM as well as on potential connections, similarities and differences between these 2 disease entities.

Both, PAH and PPCM have a high risk for morbidity and mortality but may also resolve completely. The major difficulty with PAH lies in the limited treatment options, as treatment needs to be safe for mother and child. So far the only specific treatment for severe cases of PAH such as pre-eclampsia (PE) or HELLP syndrome (H: hemolysis, EL: elevated liver enzymes, LP: low platelet count) is the delivery of the fetus.[2,3] However, despite that PAH induces massive stress on the cardiovascular system frequently with persisting damage after delivery, disease management after delivery is not well defined.

Onset of PPCM can be in the last month of pregnancy, facing the same safety problems with treatment as PAH, or in the first 6 postpartum months. It is challenging for midwifes and physicians to diagnose PPCM prepartum and postpartum, since typical symptoms of this disease, like weight gain, edema, and breathlessness, are not specific and may be misinterpreted as regular peripartum discomfort.[4] A further challenge hereby is to distinguish PPCM from pre-existing unknown (genetic) cardiomyopathies that were damasked by pregnancy.[2,5] The situation in PPCM is further compounded by the fact that acute heart failure (AHF) as it is frequently present in PPCM, needs to be treated immediately. Recommended treatment of PPCM patients consists of standard therapy for heart failure and, according to recent data, also of the prolactin (PRL) blocker bromocriptine together with thrombosis prophylaxis or anticoagulation.[5,6] If diagnosis and treatment is started in the early phase of the disease, patients have a high chance for partial or full recovery in the following months although increased risks for sudden death and relapse

remain.[2,4,5,7-9] Long-term data are scarce and recommendation for long-term management of patients with PPCM are not well defined.

In the present review we focus on PAH and PPCM, starting each disease entity with an impressive cases report. Moreover, we summarize the current knowledge on etiology, pathophysiology, management and prognosis of PAH and PPCM.

Definition and Epidemiology of PAH, PE, and HELLP Syndrome

Case Report: PE

In March 2012 a 26-year-old woman presented at our outpatient clinic for PPCM for a second opinion. After an uneventful beginning, the patient developed a severe PE towards the end of the pregnancy. Because of severely elevated blood pressure, delivery via cesarean section was indicated. After delivery the patient suffered from dyspnea, tachycardia, and dizziness, blood pressure was slightly reduced. An echocardiography, done by the tertiary hospital after the cesarean section, revealed a systolic left ventricular (LV) dysfunction. Echocardiography was repeated in our outpatient clinic, showing a moderately reduced LV systolic function with a LV ejection fraction (LVEF) of 42% (biplane Simpson method) (Fig 1A). Remarkably N-terminal pro-brain natriuretic peptide (NT-proBNP) was not elevated (124 ng/L) (Fig 1C) and the patient reported no clinical symptoms of heart failure. Heart failure therapy, including angiotensin-converting enzyme (ACE) inhibitor, beta-blocker, and diuretics, was started. Because of the medical history, the normal NT-proBNP−level (Fig 1C), a transient systolic LV dysfunction complicating PE was suspected. Therefore therapy with bromocriptine was not started. Nevertheless, the patient stopped breastfeeding soon owing to noncardiac reasons.

At the follow-up visit 2 weeks later the patient obtained a cardiac magnetic resonance imaging (MRI) and an echocardiography. Both, echocardiography and MRI showed a significant increase in LV systolic function (echocardiography, LVEF of 54%, Fig 1B), the patient was asymptomatic. The fast cardiac improvement supported the suspected diagnosis of a transient systolic LV dysfunction complicating PE. The subsequent follow-up visits were done by a private practice. In August 2017 at the 5 years follow-up visit at the outpatient clinic for PPCM, the patient was completely free of heart failure symptoms without any limitation of physical activity. Echocardiography showed a good LV systolic function with a LVEF of 56% and normal NT-proBNP levels (Fig 1C). The patient

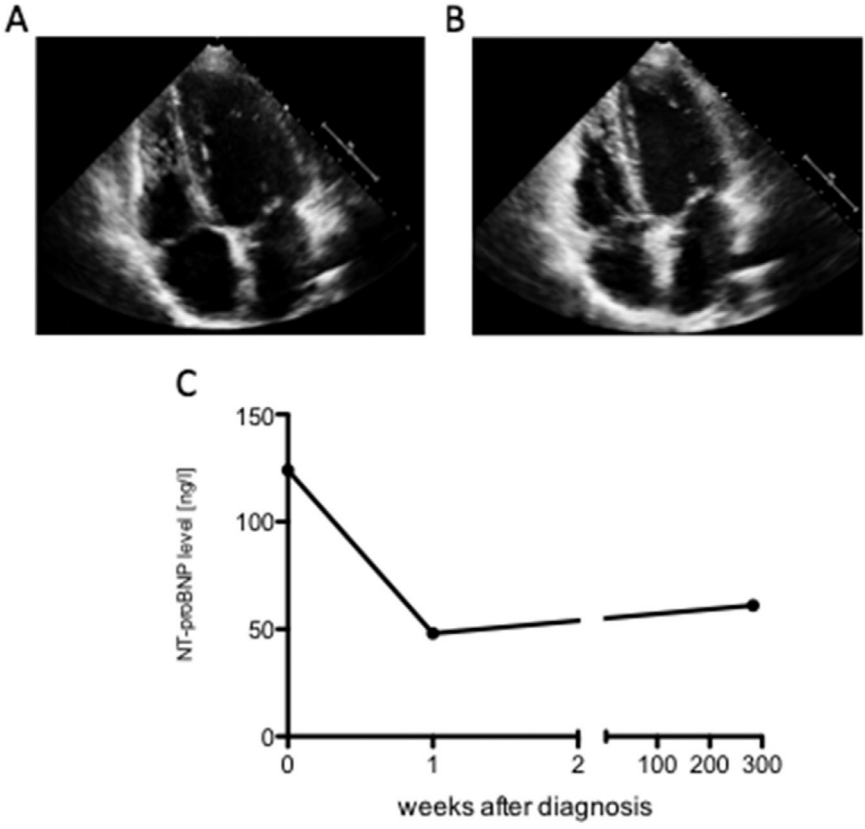

FIG 1. Echocardiography and kinetics of NTpro-BNP in a patient with transient heart failure after sever PE. Transthoracic 2-dimensional echocardiographic view at diagnosis, showing a moderately reduced LV systolic function and a dilated left ventricle (A). At 2 weeks follow-up systolic function was significantly increased and LV dilation was regressive (B). NT-proBNP level according to different time points at follow up after diagnosis in the same patient with PE (C).

reported that the heart failure medication could be reduced and finally ended a few months following the initial diagnosis.

Definition and Epidemiology of Pregnancy-Associated Hypertensive Complications

Hypertensive disorders are the most common complication of pregnancy with rising prevalence owing to increased obesity and metabolic syndrome among women in childbearing age.[10-12] In fact, between 3% and 8% of all pregnancies are complicated by hypertension in pregnancy, defined as systolic blood pressure >140 or diastolic blood pressure

<90 mmHg.[11] either new onset in pregnancy or superimposed on chronic hypertension with the most severe forms PE and HELLP syndrome.[13,14]

PE occurs in 1%-2%[11] and HELLP syndrome occurs in 0.2%-0.8% of all pregnancies. In most cases HELLP syndrome coexists with PE.[15] PE de novo or superimposed on chronic hypertension is defined as: BP >140 or >90 mmHg and 1 or more of the following criteria: proteinuria (spot urine protein or creatinine >30 mg/mmol [0.3 mg/mg] or at least 1 g/L ['2 + '] on dipstick testing or >300 mg/day in 24-hour collection), other maternal organ dysfunction or uteroplacental dysfunction with fetal growth restriction.[16,17] Typical symptoms for PE are pain in the right upper quadrant abdomen, epigastric pain, headache, nausea, and vomiting. Laboratory analyses and the clinical examination play an important role in the diagnosis of PE. Measurements of proteinuria and hypertension can be performed in early pregnancy to screen for patients with pre-existing hypertension or proteinuria. Repeating measurements, at least after 20 weeks, can help to detect PE early.[18] If the diagnosis PE is made, further blood testing is indicated to detect or rule out end-organ involvement. Especially a reduced platelet count ($<100 \times 10^9$/L) pointing to a starting HELLP syndrome, is associated with adverse maternal outcomes in women with PE.[19]

HELLP syndrome is defined as reduction of platelet count below 100,000/dL, an elevation of liver transaminases (aspartate aminotransferase or SGOT and alanine aminotransferase or SGPT) 2-fold the upper limit of normal, and an elevated lactate dehydrogenase 2-fold the upper reference limit or greater than 650 IU/L.[11] The diagnosis of HELLP syndrome requires the presence of all 3 major components (hemolysis, elevated liver enzymes, and low platelet count). If only 2 major components are present the diagnosis incomplete syndrome ("ELLP") can be made.[20] Following the diagnosis of HELLP syndrome imaging examinations (eg, ultrasound, tomography, or MR) can be helpful to rule out complications, especially hepatic impairment.[21]

PE and HELLP syndrome also bear an increased risk for heart failure,[22-24] For example, PPCM, as shown in our case report and summarized in previous review articles.[2,4] Moreover, they lead to a higher risk for CVD and heart failure later in life.[22,25]

Beside the effect of PE and HELLP syndrome on the mothers' health, recent studies report that a pathophysiological maternal milieu puts the offspring at higher risk for disease.[26] For example, the offspring of mothers with PE are more likely to have higher blood pressure and body mass index from childhood on and a higher risk for CVD in later life.[27]

Thus, hypertensive disorders of pregnancy should be classified depending on the date of onset and the severity of the hypertension (pre-existing

hypertension, gestational hypertension, PE, and "other hypertensive effects").[11] They bare a high risk of complications affecting both the pregnant women and the fetus and increase the risk for CVD later in life.

Definition and Epidemiology of PPCM

Case Report: PPCM

In October 2016, a 30-year-old woman with severely reduced LV function and advanced heart failure was transferred to Hannover Medical School from a secondary center. Four months earlier, in June 2016, the patient delivered her third child. Echocardiography revealed an LVEF of 11% (biplane Simpson method), reduced right ventricular function, and severe mitral valve regurgitation. Cardiac MRI showed comparable results regarding cardiac function (Fig 2A and B). Serum level NT-proBNP was highly elevated (Fig 2E), whereas serum level of PRL (9.4 μg/L) was in the normal range. Based on the clinical findings aforementioned, the diagnosis PPCM was made and a heart failure therapy according to the ESC guidelines for heart failure, including ACE inhibitor, beta-blocker, ivabradine, mineralocorticoid receptor antagonists, and diuretics, was started. A therapy with the PRL blocker bromocriptine was considered, but with respect to the normal PRL-level and the time lag between delivery and start of heart failure symptoms, not initiated. The patient was supplied with a wearable cardioverter-defibrillator (WCD) for primary prevention of the sudden cardiac death (SCD) owing to ventricular fibrillation and ventricular tachycardia. In the following days the clinical condition improved and the patient could be discharged after 7 days.

Almost 4 few weeks later, the patient reported still a significant limitation of physical activity corresponding to heart failure New York heart association (NYHA) class III. Echocardiography showed a severely reduced LV function without a significant improvement (LVEF: 14%, biplane Simpson method) and severe mitral valve regurgitation. Heart failure therapy was well tolerated and consistently taken. Serum level of NT-proBNP was still elevated (Fig 2E) and serum level of PRL (7.9 μg/L) was in the normal range. Based on the observation at clinic that PPCM seem to profit from bromocriptine irrespective of full-length PRL levels, it was decided to start a therapy with bromocriptine together with thrombosis prophylaxis because of the lack of improvement in LV function. Bromocriptine was prescribed for 14 days 2.5 mg twice daily, following 2.5 mg daily for 6 weeks together with low-molecular-weight heparin for venous thromboembolism prophylaxis. In January 2017, at her next visit

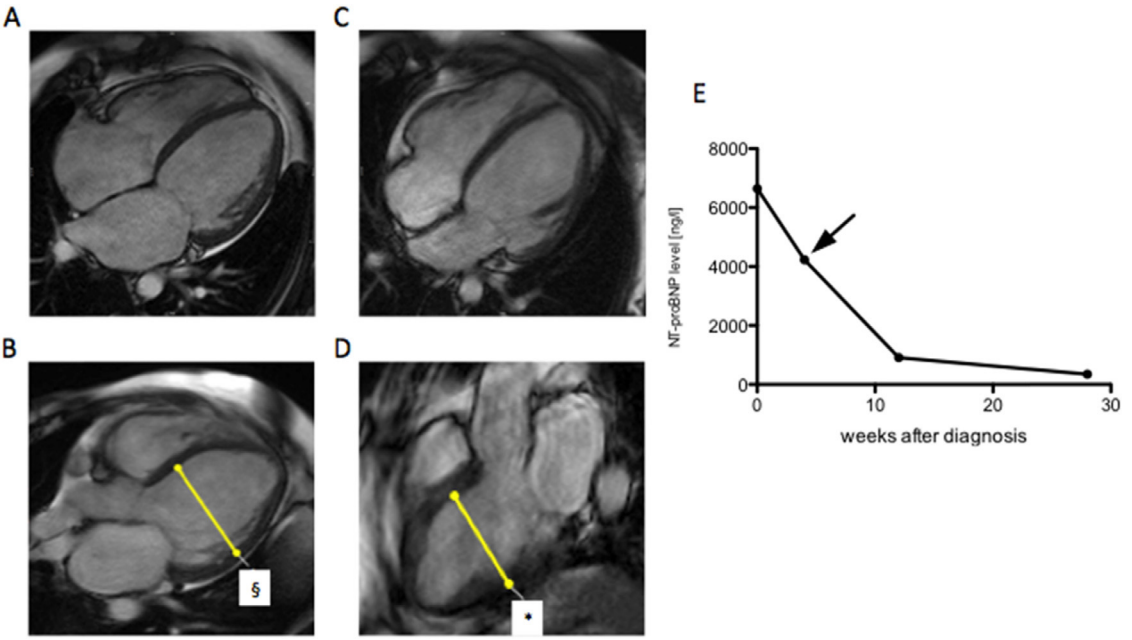

FIG 2. Cardiac magnetic resonance immaging (MRI) and kinetics of NTpro-BNP in a patient with with severe PPCM. Cardiac magnetic resonance views at diagnosis showing a severely reduced LV- and RV-function, a severe mitral valve regurgitation and a dilated left ventricle (§ = 70.5 mm) (A and B). At 6 months follow up LV- and RV-function were significantly elevated, mitral valve regurgitation and LV dilation were regressive (* = 54.2 mm) (D and F). NT-proBNP level at diagnosis and follow up in the same patient with PPCM (E). (Color version of figure is available online.)

after the treatment with bromocriptine was completed, the patient reported substantial improvement of her physical activity level, now corresponding to heart failure NYHA class II. The LV function improved significantly (LVEF: 35%, biplane Simpson method) and serum level of NT-proBNP was markedly reduced (Fig 2E). Because of mild bradycardia, the therapy with ivabradine was ended. Twenty-eight weeks after the diagnosis of PPCM the next clinical monitoring showed further improvement of LV function (LVEF 39%, biplane Simpson method) (Fig 2C and D) and serum level of NT-proBNP was further reduced (Fig 2E). Owing to the improved LV function, wearing the WCD was no longer necessary.

Definition and Epidemiology of PPCM

PPCM is a disease that emerges in the last month of pregnancy, under delivery or in the first postpartum months in women without prior history of heart disease.[2,4,7,28] PPCM has previously been considered to be a rare disease. However, more recent data indicate that PPCM is affecting around 1 in 1000 pregnancies worldwide with hotspots in Africa (1 in 100 to 1 in 1000 pregnancies) and Haiti (1 in 299 pregnancies).[2,4,7,28,29] In Western societies an increase in incidence rate of PPCM is observed over time with 1 in 4350 cases diagnosed in the United States between the years 1990-1993 to 1 in 2229 cases between the years 2000-2002.[30] In Europe (Germany) we estimate meanwhile around 1 in 1500 pregnancies.[2,4] The increased prevalence of PPCM in Western societies may be explained by socio-economic changes such as rising maternal age, fertility-assisted treatments, and multifetal pregnancies.[31] In addition, better diagnostic tools and increasing awareness, as generated also by the German PPCM registry (chaired by Hilfiker-Kleiner and Bauersachs, Hannover Germany), the African PPCM registry (chaired by Sliwa, Capetown South Africa), and the EURObservational Research Program (chaired by Sliwa, Hilfiker-Kleiner, Bauersachs, http://www.eorp.org)[32] of the European Society of Cardiology [ESC]) or the Investigations of Pregnancy-Associated Cardiomyopathy registry in the United States[33] have also contributed to detect the disease more efficiently.

The Working Group on PPCM of the Heart Failure Association of the ESC defines PPCM as follows[7]:

(1) PPCM is an idiopathic cardiomyopathy presenting with heart failure at the end of pregnancy or in the first months following delivery in women with no known pre-existing cardiomyopathies.
(2) In PPCM LV function is reduced to an LVEF $< 45\%$.

(3) PPCM is a diagnosis of exclusion meaning that other causes of heart failure should be ruled out (eg, pulmonary embolism, amniotic liquid embolism, valve disease, pre-existing cardiomyopathy, and myocardial infarction).

Most PPCM patients initially present with typical signs of AHF. Especially postpartum onset of dyspnea, tachycardia, and peripheral edema in patients without pre-existing CVDs should attract the attention of the attending physician.[5] PPCM is a diagnosis of exclusion, which means before the diagnosis PPCM can be made, other causes of heart failure should be ruled out, in particular pre-existing cardiomyopathies. However, since it is often difficult to rule out pre-existing cardiomyopathies especially if not documented and since pregnancy is a cardiac stress model and may have damasked pre-existing undetected cardiomyopathies, this feature is difficult in the clinical routine. Nevertheless, diagnostic uncertainty should never delay the start of treatment with standard medication for heart failure.

In severe cases of PPCM the patient can show signs of cardiogenic shock when admitted to the hospital (prolonged hypotension, usually referred to a systolic blood pressure below 90 mmHg in the absence of hypovolemia) in combination with signs of hypoperfusion (cold periphery, clammy skin, confusion, oliguria, metabolic acidosis, elevated serum lactate).[34] In this case diagnostics to rule out the life-threatening differential diagnosis like pulmonary embolism, amniotic liquid embolism, and myocardial infarction should be initiated immediately. In every patient with suspected PPCM the diagnostics should include blood tests including NT-proBNP and heart enzymes (troponin I and creatine-kinase-MB), electrocardiography, echocardiography, lung ultrasound, and repetitive measurements of the vital signs. Cardiac MRI can be necessary or at least provide additional information in some cases.[5] Out of these, the combination of unaltered biomarkers and unremarkable electrocardiography serve as a negative predictive marker of cardiac origin of the symptoms, but cannot confirm the diagnosis PPCM.[35,36] As aforementioned, a systolic LV dysfunction is obligatory for the diagnosis of PPCM. Therefore, echocardiography is needed as soon as possible, if PPCM is still suspected. At this point, if heart failure is assured and other causes of heart failure are ruled out or are very unlikely, the diagnosis PPCM can be made. In some cases, a cardiac MRI can provide additional information, especially when a myocarditis is suspected. Although MRI is known to be safe relating to radiation, the risks of fetal gadolinium exposure are still unknown. Therefore gadolinium-based contrast agents should be avoided in pregnant PPCM

patients.[37] If the result of the cardiac MRI is compatible with the diagnosis myocarditis, a myocardial biopsy can be performed to confirm or exclude a myocarditis, but usually treatment will be similar in PPCM and peripartum myocarditis so that it has limited diagnostic value in PPCM.[38]

Pathophysiology of Pregnancy-Associated Hypertensive Complications and PPCM With Potential Link Between the Two Entities, as well as Influence of Comorbidities

Pregnancy-Associated Hypertensive Complications

The pathophysiology of pregnancy-associated hypertensive complications such as PE are still not completely understood. However, it is well known that the placenta is of central importance, since multiple deficiencies in placentation (eg, deficits in the process of cytotrophoblast differentiation, activation of the maternal immune system) lead to an inadequate spiral artery remodeling.[39] This inadequate spiral artery remodeling leads to intermittent placental perfusion causing "hypoxic-reoxygenation injuries" and oxidative stress (Fig 3).[40] Circulating factors such as cytokines, apoptotic factors, and antiangiogenic factors, that is, tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-1α, IL-1β, Fas ligand, oxidized lipid products, neurokinin B, asymmetric dimethylarginine, soluble fms-like tyrosine kinase-1 (sFlt-1), and endoglin are elevated in PE and are thought to be of pathophysiological relevance (Fig 3).[41,42] They seem to induce a systemic endothelial dysfunction affecting both, the mother and the fetus. However, since the diseased placenta seems to be the major cause for this disorder and medical therapies are very limited in pregnancy, delivery of the baby and removal of the placenta remains frequently the only cure of PE to date.[43]

Meanwhile it is well known, that the delivery may not completely solve the problem since PE patients continue to have a higher risk for cardiovascular complications. Indeed, persistent cardiovascular abnormalities and inflammatory responses, suggest that in women with PE regular monitoring of blood pressure, urine albumin level, fasting glucose, and lipid panel together with a treatment according to the national guidelines for CVD prevention should be implemented.[43] This should be associated with lifestyle modifications (smoking cessation, healthy diet, exercise, and weight loss) in order to minimize (cardiovascular) risk in these women.[43] Remarkably it is suggested that vasoinhibin, an N-terminal

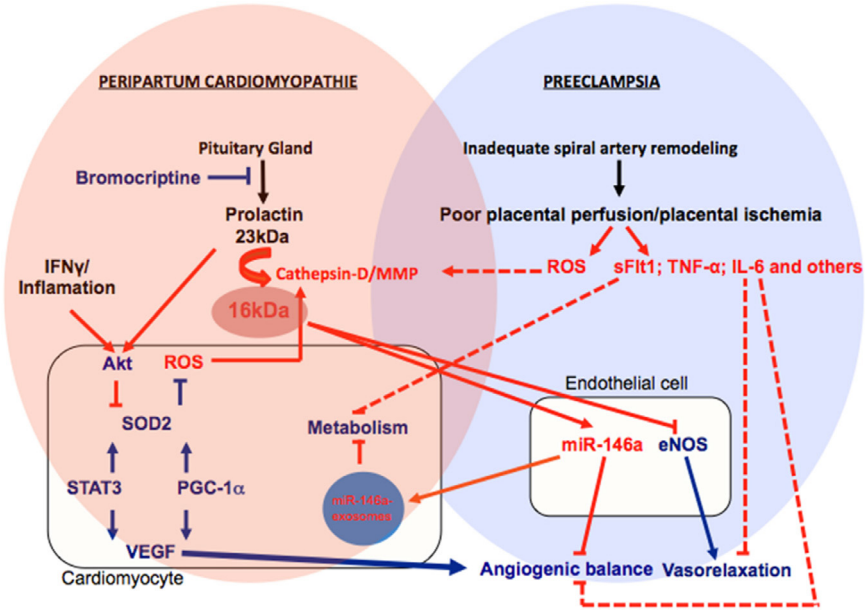

FIG 3. Schematic illustration of the pathophysiological mechanisms in PPCM, leading to the generation of antiangiogenic 16 kDa prolactin, the pathophysiological mechanisms in PE where placental ischemia lead to endothelial and cardiovascular dysfunction and a potential overlap between in pathophysiologies between PE and PPCM. (Color version of figure is available online.)

16 kDa fragment (16-kDa PRL) of the nursing hormone PRL may also play an important role in PE (Fig 3). It had been hypothesized that predominant decidual production of 16-kDa PRL over that of the full-length nursing hormone 23-kDa PRL induces an antiangiogenic process with a shallow invasion of the spiral arteries by the endovascular cytotrophoblast (Fig 3). This may promote a high-resistance arteriolar system and placental ischemia or hypoxia leading to endothelial cell dysfunction and increased oxidative stress.[44] This hypothesis is supported by the observation that blood and urinary levels of 16-kDa PRL directly correlate with adverse outcome of PE and HELLP syndrome patients.[45] Finally, the endothelial dysfunction and the high level of antiangiogenic factors present in women with pregnancy-associated hypertensive disorders, may predispose to heart failure, transiently as it is reported in case at the beginning of this article (Fig 1) or in more severe forms such as PPCM.[2,4]

Peripartum Cardiomyopathy

Over the past 2 decades research on PPCM has steadily increased providing more insights in the etiology and pathophysiology of the disease.

In this regard a number of risk factors such as low selenium levels, various viral infections, autoimmune reactions, tocolytic therapies, smoking, drug abuse, age, sex of the fetus, or multiple pregnancies were suspected to be causally related to PPCM.[28,46] Nevertheless, in many patients such obvious risk factors cannot be found as also women at low-risk age (between 20 and 30 years of age) develop the disease at their first pregnancy without carrying any of the aforementioned risk factors. More recent research suggests that even though triggering events might be of multiple origins, they all may converge on a common pathway, which involves unbalanced oxidative stress and the generation of the antiangiogenic 16-kDa PRL (Fig 3).[2,4]

It is interesting to note that during pregnancy physiologically rising oxidative stress leads to increased production of reactive oxygen species, which is usually compensated by an increase of the total antioxidant capacity.[47] One of the mechanisms, which enhances the antioxidant capacity is an increased expression of mitochondrial superoxide dismutase 2 (SOD2). The signaling pathway, which is responsible for the upregulation of SOD2 includes signal transducer and activator of transcription 3 (STAT3) and peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) (Fig 3).[48,49] In PPCM this balance, between oxidative stress and the total antioxidant capacity is impaired, leading to rising oxidative stress towards the end of pregnancy and in the early postpartum phase.[48,50] A fatal combination in the pathophysiology of PPCM seems to be that at one point increased oxidative stress meets high circulating levels of the nursing hormone PRL, periodically released from the pituitary gland. During pregnancy and specifically postpartum PRL levels rise up to 200 ng/mL (normal PRL levels in women: 2.79-23−3 ng/mL).[51] The enhanced oxidative stress in PPCM patients promotes the activation of proteolytic enzymes like cathepsin D or matrix metalloproteinase, which can process the 23-kDa nursing hormone into the shorter 16-kDa PRL form (Fig 3).[52] In contrast to the 23-kDa PRL, which is known to have proangiogenic effects, the 16-kDa PRL is an antiangiogenic factor (Fig 3).[53] The antiangiogenic effect of 16-kDa PRL results from multiple effects on endothelial cells which include the induction of apoptosis and disruption of capillary structures as well as prevention of migration and proliferation of endothelial cells.[54] Moreover, 16-kDa PRL can block the Ca^{2+}-mediated activation of endothelial nitric oxide synthase (eNOS), which attenuates vasorelaxation and angiogenesis.[55,56] Furthermore 16-kDa PRL signals directly into endothelial cells where it upregulates the microRNA-146a (miR-146a) which mediates many of the adverse effects of 16-kDa PRL to the cardiovasculare system (Fig 3).[57]

Additional antiangiogenic factors such as sFlt-1 may act in concert with the 16-kDa PRL to disturb the angiogenic balance during the peripartum phase, thereby even worsening the metabolic shortage in the heart.[50] Moreover, high sFlt-1 during PE might be a predisposing factor for PPCM and thereby connect PAH causally to PPCM (Fig 3). Interestingly, it has been reported that 18.6% of women develop postpartum hypertension.[58] Among them almost half develop the condition de novo in the postpartum periode without having a history of PAH showing similar clinical risk factors and postpartum plasma angiogenic profile to women with PE.[58] The reason for such de novo postpartum hypertension is unclear, it may result from subclinical or unresolved PE or it may represent a postpartum-related pathology that in fact could predispose to PPCM. Indeed, almost half of PPCM patients in Germany, Japan, and the United States had a history of PAH.[2,8,33,59] High degree of inflammation, frequently present in PPCM patients, seems to further accelerate disease severity.[60] Most strikingly, all these different pathophysiological aspects in the various experimental models seem to be cured by simply blocking PRL with bromocriptine (Fig 3).[48,50,57,60]

Higher levels of the PRL cleaving enzyme cathepsin D, the cleaved 16-kDa PRL and the miR-146a are also observed in PPCM blood compared to healthy postpartum controls.[48,57] Moreover, several healing attempts supported the idea that PRL blockade in addition to heart failure medication prevents PPCM in patients and promotes healing of acute PPCM.[48,61-63] Moreover, a small prospective pilot trial with 20 patients with severe PPCM,[64] a recent larger multinational study with 34 PPCM patients with subsequent pregnancies (SSP)[6] and a recent randomized multicentric trial with 63 severely affected PPCM patients[9] also confirm a potential benefit of bromocriptine treatment in addition to standard therapy for heart failure in PPCM.

Clinical Management of Pregnancy-Associated Hypertensive Complications and PPCM

Pregnancy-Associated Hypertensive Complications

At time of diagnosis the complete clinical work up, that is, blood test including platelet count, liver transaminases, lactate dehydrogenase and hemoglobin concentration, urine testing, and ultrasound, should be completed in patients suspected of PAH. In case of >37 weeks of gestation or suspected abruptio placentae, delivery should be induced. In case of >34 weeks of delivery, delivery should only be induced if one of the complications listed in the Table is present. Furthermore clinical evaluation of

TABLE. Indications for delivery in patients with PAH < 37 0/7 weeks of gestation.

Progressive labor
Amniorrhexis
Estimate of fetal weight < than fifth percentile in ultrasound
Oligohydramnios (persistent amniotic fluid index less than 5 cm)
Persistent biophysical profile ≤ 6/10

the status of the fetus is absolutely necessary and should include imaging examinations to evaluate fetal weight, amniotic fluid index, and nonstress test (NST). If NST is nonreactive the biophysical profile should be done. Amniotic fluid index should be re-evaluated at least once a week, whereas NST can be monitored in 2 weeks intervals, and fetal weight can be monitored in 3 weeks intervals. Depending on the findings in these tests and coexisting diseases, the frequency of these tests has to be elevated.[65]

Maternal symptoms, blood pressure and fetal movement should be monitored daily by the mother, which should be trained for this reason. Blood pressure, clinical examination, and urine testing should be repeated at each clinical visit. The blood tests should be repeated at least once a week. In case of pathologic findings, especially regarding the status of the fetus or symptoms of severe PE, the patient should be hospitalized immediately.[65]

In case of severe hypertension a medical antihypertensive treatment has to be started, as severe hypertension is an independent risk factor for cardiovascular complications like for example stroke.[66] Antihypertensive medication considered safe in pregnancy are hydralazine, labetalol, or any calcium channel blocker.[3] For nonsevere hypertension, there are no prospective randomized studies in pregnancy to define at what level of hypertension a treatment should be started to lower the risk of cardiovascular complications for mother and fetus. Therefore, a medical treatment in nonsevere hypertension is always an individual decision and the comorbidities should always be taken into consideration. Regarding the different antihypertensive drugs, there is no significant difference between a treatment with hydralazine, labetalol, or any calcium channel blocker regarding efficacy and safety.[67]

It is important to note that hypertension in the postpartum period is relatively common and is associated with prolonged hospitalization.[58] Complicating to this fact can be that a PAH patient displays normal blood pressure immediately after delivery but becomes hypertensive again in the weeks following delivery.[58] In addition, as reported earlier, postpartum hypertension may also develop de novo in women without having a history of PAH suggesting that blood pressure control in the first postpartum months should be done routinely.

In their review "Management of hypertension before, during, and after pregnancy" James and Nelson-Piercy[68] suggest the following for postpartum management for PAH patients with postpartum hypertension: "Methyldopa should be avoided postpartum because of the risk of postnatal depression. Our first line agent is atenolol, plus nifedipine, or an ACE inhibitor if another agent is required. Women with gestational hypertension, or PE, are usually able to stop all antihypertensive medication within 6 weeks postpartum. Those with chronic hypertension can resume their prepregnancy drugs. Diuretics, however, are usually avoided if the woman wishes to breast feed because of increased thirst. Proteinuria in pre-eclamptic women will usually remit by 3 months postpartum, in the absence of any underlying renal abnormality." They suggest that women who developed PAH during pregnancy have an increased risk for developing PAH again in SSP and should therefore be closely monitored for blood pressure in following pregnancies.[68] Finally, as mentioned previously, women who experienced PAH are at a higher risk for developing CVD later in life and should be regularly examined by a cardiologist and should have at least an annual blood pressure measurement by an experienced medical person.[68] Therefore, we recommend a close monitoring of blood pressure after delivery. If blood pressure is persistently elevated the antihypertensive treatment should be continued. There is little data regarding the choice of agent,[69] we recommend a treatment according to the guidelines for the management of arterial hypertension.[70] For the choice of the antihypertensive agent, one has to consider whether the patient is breastfeeding or not and if the agent is safe for breastfeeding. A special emphasis should be put on counseling women with PAH who wish to become pregnant again as postpartum antihypertensive medication may be harmful for the fetus and because they face a higher risk for relapse of PAH in following pregnancies.

Peripartum Cardiomyopathy

The clinical management of PPCM differs, depending on the state of pregnancy and the cardiopulmonary distress of the patient. In general, AHF owing to PPCM has to be treated in a multidisciplinary approach. Especially cardiologists and gynecologists need to work closely together with respect to the health status of mother and fetus. Often neonatologists, anesthetists, and cardiac surgeons are also involved in the treatment of acute PPCM.[4] The different concepts are lined out later.

Heart Failure During Pregnancy. If the diagnosis PPCM is made during pregnancy, drugs with fetal toxicity, that is, ACE inhibitors,

angiotensin receptor blockers, and mineralocorticoid receptor antagonists should be avoided. Beta-blockers are the only class of heart failure drugs to be relatively safe during pregnancy and they should be used if PPCM develops during pregnancy.[3] Beside the treatment of heart failure, the systolic function should be monitored closely via echocardiography. In patients with a high risk for PPCM, for example because of a PPCM in a previous pregnancy, we recommend performing echocardiography from the 20th gestation week onwards every 4 weeks and from the 30th gestation week every 2 weeks onwards.[5] Mode of delivery should be planned and take place in an experienced center for the clinical management of PPCM.[5]

Heart Failure Postpartum in Patients Without Cardiopulmonary Distress. If the diagnosis PPCM is made postpartum, the treatment differs whether the patient shows signs of cardiopulmonary distress or not. Patients without cardiopulmonary distress should be treated according to the ESC guidelines for heart failure. Simultaneously to the heart failure drugs the PRL blocker bromocriptine should be considered in these patients since, as outlined earlier, it blocks a disease specific pathomechanisms and has been promising in first clinical tests.[4,6,9,64] In addition, a retrospective population-based study on treatment and outcome of PPCM describes blocking of PRL as one of the parameters predicting recovery,[8] and a systematic review confirmed bromocriptine as a useful agent to improve outcome of PPCM.[71,72]

So far we recommend, depending on our experience and the recent data, a bromocriptine treatment in all PPCM patients. Dose and duration of the application should vary, depending on the extent of the cardiopulmonary distress, according to the PPCM-treatment scheme from Hannover Medical School.[9] During application of bromocriptine prophylactic anticoagulation with heparin or bivalirudine should be given, as thromboembolic events have been reported during the use of bromocriptine.[73-75] Arrigo et al[76] named this therapeutic approach the BOARD concept (bromocriptine, oral heart failure therapies, anticoagulants, vasorelaxing agents, and diuretics).

Heart Failure Postpartum in Patients With Cardiopulmonary Distress. The use of catecholamines is known to have adverse effects in patients with advanced heart failure and is associated with a higher 6-month mortality rate in heart failure patients.[77] Data from the German PPCM registry suggests that the use of inotropes (eg, dobutamine) is associated with an adverse outcome in PPCM patients with severe heart failure.[78] Therefore, catecholamines should be avoided in PPCM patients.[4,5] Instead of application of catecholamines, in case of massive cardiopulmonary distress,

mechanical circulatory support devices for example, Impella, intra-aortic balloon pump, and veno-arterial extracorporeal membrane oxygenation should be considered in PPCM patients with cardiogenic shock since with the use of mechanical circulatory support devices, the need for catecholamines often decreases significantly.[5] The choice of the support device depends on the oxygenation status of the patient. As some devices only provide circulatory support (Impella, intra-aortic balloon pump) and other devices work as circulatory support and provide oxygenation, the choice of the device is always an individual decision, especially as there is no valid data regarding mechanical circulatory support devices in PPCM.

In addition, we recommend higher and longer dosage of bromocriptine according to the PPCM-treatment scheme from Hannover Medical School[9] in patients with an LVEF < 25% or severe cardiopulmonary distress. In critically ill patients, we recommend sequential measurements of PRL levels. If necessary for effective suppression of PRL level, the bromocriptine dosage should be increased up to 10 mg twice daily. At least prophylactic anticoagulation is also necessary during the entire treatment with bromocriptine independent of the dosage.

Risk for Sudden Death in Patients With Postpartum PPCM. In many cases PPCM patients show a severe reduced systolic LV function with a LVEF < 35%. It is known that a LVEF < 35% is associated with an increased risk of SCD owing to ventricular arrhythmias. Therefore, the ESC guidelines recommend implantation of an implantable cardioverter defibrillator (ICD) for primary prevention in patients with an LVEF <35% under best medical treatment.[79] When it comes to the decision whether an ICD should be implanted in PPCM patients one has to consider the high potential for recovery of systolic function in PPCM. In this situation, when the risk for SCD is increased but the patient has the potential for recovery of systolic function, wearable cardioverter defibrillator (WCD; LifeVest, Zoll, Pittsburgh, PA) is a useful tool to protect the patient from SCD until a definitive decision about ICD implantation can be made.[80] As ventricular arrhythmias did occur after 30-160 days in a German multicenter analysis, we recommend wearing the WCD for 3-6 months. Interestingly, in the aforementioned study,[80] Ventricular fibrillation did occur in 1 patient with a LVEF >45%. Therefore, the authors recommend completing the wearing time of 3-6 months independently of the LVEF.[81]

Subsequent Pregnancy and Contraception. The most frequently asked questions by PPCM patients, their partners and their treating physicians, consider SSP. The literature is quite clear and reports a substantial risk

for worsening heart failure and death in SSP in PPCM patients especially if heart function was not normalized prior SSP.[82-84] In case of a SSP, the PPCM patients should be monitored closely in a multidisciplinary approach. We recommend frequent clinical and echocardiographic monitoring of the heart failure symptoms and the systolic function and delivery if heart function is worsening.[4] If the patient remains stable she may have a normal vaginal delivery.[4] However, no matter if the patient displays stable or decreasing cardiac function after delivery, we recommend immediate start of bromocriptine and heart failure medication and anticoagulation as soon as the patient is hemodynamically stable.[6]

If a SSP is considered to be unsafe or children are not desired, we strongly recommend contraceptive use. So far there is sparse data regarding the safety of the different methods of contraception in PPCM. As the use of hormonal methods of contraception in women with cardiac disease is associated with cardiovascular complications,[85] we suggest intrauterine devices, which are reported to be safe in women with cardiac disease.[86] As all of these studies included women with several forms of cardiac diseases the safety of the different methods of contraception in PPCM therefore requires further clarification.

Conclusion

Recent studies contributed to the understanding of pathophysiology and clinical management of PPCM and pregnancy-associated hypertensive complications. Angiogenic imbalance and endothelial damage play an important role in both entities and are connections in the pathophysiology between these entities, establishing a potential causal link between PAH and PPCM. Patients with PAH should be monitored closely. Severe hypertension should always be treated with antihypertensive medication allowed in pregnancy, whereas data for nonsevere hypertension in pregnancy is sparse, and the decision at what point an antihypertensive treatment should be started depends on the treating physician. Delivery remains still the only efficient way to treat severe PAH but even after delivery antihypertensive condition may proceed and adequate antihypertensive medication and regular long-term cardiovascular monitoring is recommended in patients who experienced PAH in pregnancy. In AHF owing to PPCM, standard heart failure medication and treatment with the PRL blocker bromocriptine and antithrombotic therapy should always be considered. SSP bears a high risk for a relapse of heart failure and therefore counseling of patients with PPCM who wish to become pregnant again is highly recommended. If a patient is pregnant with an SSP we

recommend the use of the PPCM-treatment scheme from Hannover Medical School[9] in acute PPCM and in SSP. Nevertheless many aspects of the pathophysiology and the clinical management of PAH and PPCM are still unclear. Especially biomarkers and diagnostic methods to identify patients with a high risk of developing a PPCM or to make prognostic statements for individual PAH or PPCM patients would be of great significance. Therefore further studies are necessary to elucidate these questions and to help improving the clinical management and prognosis of PPCM patients.

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Cardiovascular problems during pregnancy are increasing worldwide. Pregnancy associated hypertensive complications such as preeclampsia or peripartum cardiomyopathy are potentially life threatening in healthy women.

Several perspectives can be taken from this detail manuscript.

First, angiogenic imbalance and endothelial damage play an important role in both preeclampsia or peripartum cardiomyopathy.

Second, patients with pregnancy associated hypertension should be monitored closely. Severe hypertension should be treated with antihypertensive medication allowed in pregnancy. In addition, delivery remains still the only efficient way to treat severe pregnancy associated hypertension but even after delivery adequate antihypertensive medication and regular long-term cardiovascular monitoring is recommended in patients who experienced pregnancy associated hypertension.

Third, in acute heart failure due to peripartum cardiomyopathy, standard guideline therapy for heart failure as well as prolactin blocker bromocriptine and antithrombotic therapy should be utilized. Subsequent pregnancies are associated with heart failure relapse, thus, it is important and highly recommended to counsel patients of patients with peripartum cardiomyopathy that wish to become pregnant again.

Finally, the utilization of biomarkers in order to assess prognosis as well as diagnosis in patients with high risk to develop peripartum cardiomyopathy is a developing field that may prove to be a great significance.

I want to thank the authors for this excellent manuscript and I hope the readers of the Journal will find a very helpful guide of the different aspects on diagnosis and management of pregnancy associated hypertension and peripartum cardiomyopathy.