Pathophysiology and epidemiology of peripartum cardiomyopathy

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Abstract | Cardiovascular diseases are a major cause of complications in pregnancy worldwide, and the number of patients who develop cardiac problems during pregnancy is increasing. Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease that emerges towards the end of pregnancy or in the first months postpartum, in previously healthy women. Symptoms and signs of PPCM are similar to those in patients with idiopathic dilated cardiomyopathy. The incidence varies geographically, most likely because of socioeconomic and genetic factors. The syndrome is associated with a high morbidity and mortality, and diagnosis is often delayed. Various mechanisms have been investigated, including the hypothesis that unbalanced peripartum or postpartum oxidative stress triggers the proteolytic cleavage of the nursing hormone prolactin into a potent antiangiogenic, proapoptotic, and proinflammatory 16 kDa fragment. This theory provides the basis for the discovery of disease-specific biomarkers and promising novel therapeutic targets. In this Review, we describe the latest understanding of the epidemiology, pathophysiology, and novel treatment strategies for patients with PPCM.

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Introduction

Peripartum cardiomyopathy (PPCM) is increasingly recognized as an important condition that can complicate pregnancy. This disease is associated with a high morbidity and mortality,[1–4] but its aetiology remains unknown. In 2010, the Working Group on PPCM from the Heart Failure Association of the ESC proposed the following definition of PPCM: "Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%."[4] PPCM phenotypically resembles the cardiac characteristics of dilated cardiomyopathy (DCM), but the condition is considered an independent disease, distinct from other cardiomyopathies.[1]

Physicians are often faced with the difficulty of distinguishing between peripartum discomfort in healthy women (such as fatigue, mild shortness of breath, or mild oedema), and the pathological symptoms of PPCM. Importantly, PPCM can present either very dramatically, with acute heart failure necessitating admission to intensive care, or subtly over several weeks. Generally, however, PPCM manifests in the final weeks of pregnancy or within the first months after delivery in previously healthy women (Figure 1), mainly through typical symptoms of heart failure, such as dyspnoea, exercise intolerance, cough, and orthopnoea.[3–7] Nonspecific symptoms of cardiac congestion, such as abdominal discomfort, pleuritic chest pain, and palpitations, can also occur. Establishing a diagnosis of PPCM, therefore, relies on a high index of suspicion, because early signs and symptoms of heart failure are often not easy to distinguish from peripartum-associated physiological discomfort, which can lead to delayed diagnosis.[2–4] In a retrospective review and analysis of 182 patients with PPCM, diagnosis was delayed by >1 week in 48% of patients who later experienced a major adverse event (death, heart transplantation, or defibrillator implantation).[8] A thorough medical history of the exact onset of symptoms in relation to pregnancy, and subsequent diagnostic confirmation of left ventricular systolic dysfunction by echocardiography, MRI, or both, are important. Furthermore, a thorough evaluation is necessary to eliminate other potential cardiac and noncardiac explanations for a patient's clinical presentation.

Various underlying mechanisms have been proposed, including a low selenium level, viral infections, stress-activated cytokines, inflammation and autoimmune reactions, and a pathological response to haemodynamic stress.[3,9] Data now suggest a common pathway on which various aetiologies that induce PPCM might converge. This pathway includes unbalanced oxidative stress and a high level of the nursing hormone prolactin, which leads to the production of an angiostatic and proapoptotic 16 kDa fragment of prolactin that seems to initiate and propagate the disease.[10,11] The 16 kDa form of prolactin mainly affects the endothelium and might, together with additional antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFLT-1; also known as vascular

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Key points

- Peripartum cardiomyopathy (PPCM) is defined as idiopathic systolic dysfunction in peripartum women
- To make a diagnosis of PPCM, other possible causes of heart failure in peripartum women, such as genetic forms of dilated cardiomyopathy, need to be excluded
- The incidence and prognosis of PPCM vary according to socioeconomic and genetic factors
- The aetiology of PPCM is unknown; risk factors might include pre-eclampsia, twin pregnancies, and African ethnicity
- A possible pathophysiological mechanism for PPCM is the production of a 16 kDa fragment of prolactin; blocking prolactin is, therefore, a potential therapeutic target

endothelial growth factor receptor 1), disturb the angiogenic balance in the peripartum phase, thereby promoting metabolic shortage in the heart, with potential negative effects on cardiac function.[11,12]

In this Review, we not only summarize the current understanding of the epidemiology and pathophysiology of PPCM, but also specifically attempt to interweave the experimental and clinical observations in a 'bed-to-bench-and-back' approach. We have shown that continuously high serum levels of IFN-γ and prolactin are associated with an increased inflammatory status and adverse outcomes in patients with PPCM.[13] In experimental studies, we showed that IFN-γ, prolactin, or both, promote cardiac inflammation and might, therefore, have a causal role in impaired prognosis.[14] Furthermore, a high percentage of patients with PPCM in Germany, Japan, and the USA have a history of hypertensive disorders during pregnancy.[7,12,15] Accordingly, we provided experimental evidence that such a history can, indeed, predispose women to PPCM via a mechanism involving sFLT-1 and insufficient upregulation of vascular endothelial growth factor (VEGF) in the heart.[12] Overall, we present novel insights into the pathophysiology of the disease and the potential consequences for the clinical management of patients with PPCM.

Epidemiology

The current epidemiological profile of PPCM is largely unknown, with most data coming from Africa, Haiti, and the USA. The incidence of PPCM seems to be variable, depending on the geographical region, ethnic background, and inclusion criteria of the study.[3,16–18] Epidemiological studies are complicated by the potential difficulty in initially distinguishing PPCM from other forms of cardiomyopathy, such as familial or pre-existing idiopathic DCM. The diagnosis occasionally changes after family screening and genetic testing have been performed, particularly if known mutations in genes that can cause cardiomyopathy emerge. However, owing to difficulties in performing broad genetic tests in cohorts of individuals with PPCM, genetic forms of cardiomyopathies might have been included in many of the published case series and epidemiological studies of PPCM.

The Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project[19] was a cross-sectional study of 14,323,731 hospitalizations for pregnancy in the USA between 2004 and 2006. The rate of hospitalizations for cardiomyopathy in the postpartum period was 0.46 per 1,000 deliveries (0.18 for apparent PPCM, and 0.28 for other cardiomyopathies).[19] Myocardial disorders were rare during delivery hospitalizations (0.01%), but were not uncommon among postpartum hospitalizations (4.2%).[19] Data suggest a wide variation in the estimated incidence of PPCM according to geographical region: 1 per 299 live births in Haiti,[20] 1 per 1,000 live births in South Africa,[21] and 1 per 1,149–4,000 live births in the USA.[16,22] The incidence of PPCM in Asia, Australia, and Europe is uncertain and requires epidemiological study. The reason for this geographical variation in the incidence of PPCM is unknown, but might be linked to ethnic and socioeconomic factors.[16] In one study, a large difference in the incidence of PPCM was identified between ethnic groups in the USA: 1 per 1,421 in African–American women, 1 per 2,675 in Asian women, 1 per 4,075 in white women, and 1 per 9,861 in Hispanic women.[16] In another study from the USA, a 15-fold higher incidence of PPCM was reported in African–American women than in women of other ethnicities.[23]

Disease presentation in different ethnic groups might influence left ventricular recovery and survival. Outcomes in African–American patients diagnosed with PPCM were similar to those in Haiti and South Africa, but lower than those in white US women.[24,25] Socioeconomic factors might limit access to timely and advanced medical care. However, in the US and South African studies, patients of all ethnic groups had a similar rate of optimal

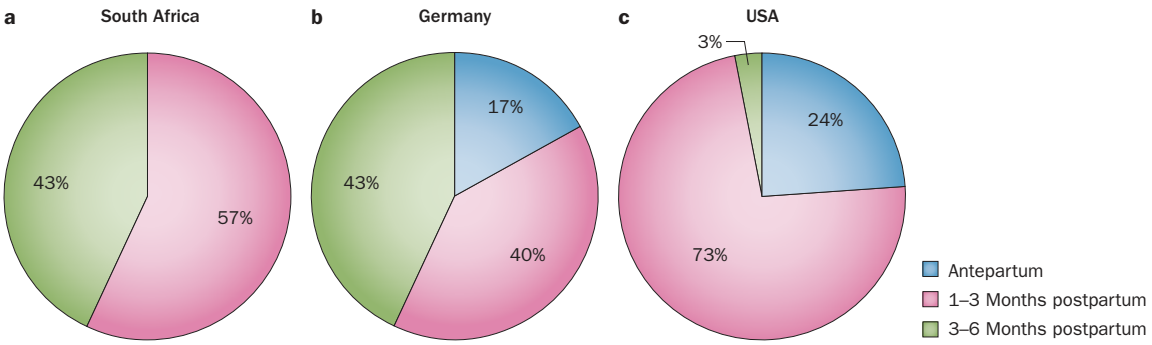

Figure 1 | Time of onset of symptoms of peripartum cardiomyopathy according to country. **a** | South Africa.[9] **b** | Germany.[7] **c** | USA.[6]

drug therapy, including angiotensin-converting-enzyme inhibitors and β-blockers.[24,26]

Interestingly, an increase in the incidence of PPCM has been reported in the USA, from 1 per 4,350 in 1990–1993, to 1 per 2,229 in 2000–2002.[27] This trend might be attributable to a rise in maternal age, an increase in multifetal pregnancies owing to access to reproductive techniques, or possibly improved recognition and diagnosis of the disease. Enhanced awareness has been promoted by the ESC, the activities of a specialized working group on PPCM, and the international registry of patients with PPCM as part of the EURObservational Research Programme.[28] Worldwide, awareness has been promoted via many publications and Internet-based reporting facilities.[29,30] The number of original and review publications on the topic of PPCM has increased substantially over the past 20 years.[31] A further increase in awareness and reporting can be expected with the EURObservational Research Programme,[28] which now has >80 centres in 50 countries registered.

Pathophysiology

Familial and genetic predisposition

Pregnancy places physiological stress on the human heart and, unsurprisingly, can unmask genetic forms of cardiomyopathy. The increased incidence in particular geographical regions suggests that genetic predisposition might have an important role.[3] A few instances have been reported of patients with PPCM who have mothers or sisters who have also had the condition.[32–36] A subset of patients with PPCM have been identified as carriers of mutations associated with familial forms of DCM, involving mutations in *MYBPC3*, *MYH6*, *MYH7*, *PSEN2*, *SCN5A*, *TNNC1*, and *TNNT2*.[36–38] Noncompaction cardiomyopathies have also been reported as possible underlying genetic forms of PPCM,[39–41] but this phenotype seems to be transient in some patients.[42] Therefore, a subset of patients with PPCM might, in fact, be presenting with an initial manifestation of familial DCM. However, additional genetic factors, independent of the known cardiomyopathy-inducing mutations, might also contribute to susceptibility to peripartum heart failure. The importance of distinguishing between genetic and nongenetic forms of peripartum heart failure derives from early epidemiological studies that indicated that PPCM in women with a family history of cardiomyopathies have a poor prognosis—a feature that might affect risk stratification and clinical management of these patients.[7] In our expert experience, however, most women with PPCM report no family history of cardiomyopathy. Therefore, the taking of a detailed family history is important in patients with peripartum heart failure, but routine genetic testing might be indicated only in those with a history of cardiomyopathy.

Oxidative stress and angiogenic imbalance

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS: reactive molecules that contain oxygen ions and peroxides are highly reactive owing to the presence of unpaired valence-shell electrons) and a biological system's capacity to detoxify ROS or repair the resulting damage. The level of oxidative stress rises during pregnancy, and late pregnancy is associated with the formation of particles that are susceptible to oxidation (high LDL-cholesterol level) and an increase in oxidative damage.[43] The biological function of increased ROS production might be to increase maternal defence against pathogens during pregnancy, when the immune system is compromised and the risk of infection, particularly during delivery, is high. However, in normal pregnancy, increased ROS production is paralleled by an increase in antioxidant capacity, with an early postpartum peak in healthy women.[43] Moreover, organ-specific antioxidant defence mechanisms seem to be particularly important in the peripartum phase. In the heart, for example, the expression of antioxidant enzymes, such as mitochondrial superoxide dismutase [Mn] (SOD2), is increased.[11,12] Major signalling pathways that are responsible for the upregulation of SOD2 include signal transducer and activator of transcription 3 (STAT3) and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α).[11,12] The precise balance between oxidative and antioxidant capacity, late in pregnancy and early postpartum, is critical to maintain maternal health (Figure 2). A compromised antioxidant defence system results in a shift towards increased oxidative stress, which predisposes to PPCM.[11,12] An efficient antioxidant defence might even be relevant to the long-term cardiovascular health of women, particularly those of high parity or those at high risk of cardiovascular disease (women with diabetes mellitus or hypertension, or who are obese).

Prolactin and its cleaved products

PPCM, being a disease of late pregnancy and early postpartum, might be triggered by factors specifically present in the late-gestational period. The nursing hormone prolactin is among the prominent hormones in the peripartum phase, and large quantities of prolactin are released from the pituitary gland into the circulation during lactation.[44] Prolactin can exert opposing effects on angiogenesis depending on proteolytic processing of the potentially proangiogenic, full-length, 23 kDa form of the hormone into an antiangiogenic, 16 kDa derivative.[44] The 16 kDa form of prolactin, also called vasoinhibin, was initially identified as a potent antiangiogenic factor.[45] This prolactin variant is generated from full-length prolactin by cathepsin D[46] or other proteolytic enzymes, such as matrix metalloproteinases (MMPs): MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13 can cleave human prolactin into biologically functional 16 kDa prolactin.[47] An important role of MMPs in the generation of 16 kDa prolactin in PPCM is supported by studies showing that the serum level of MMP-2 is significantly higher in women with PPCM than in matched pregnant controls.[13] Furthermore, the MMP-3 level was substantially increased in the hearts of mice with PPCM as a result of cardiomyocyte-specific knockout of *Stat3* (*Stat3*$^{-/-}$).[11] Interestingly, lowering of oxidative stress using the SOD2-mimetic MnTABP [Mn(III)tetrakis(4-benzoic acid) porphyrin chloride] in *Stat3*$^{-/-}$ mice provided only

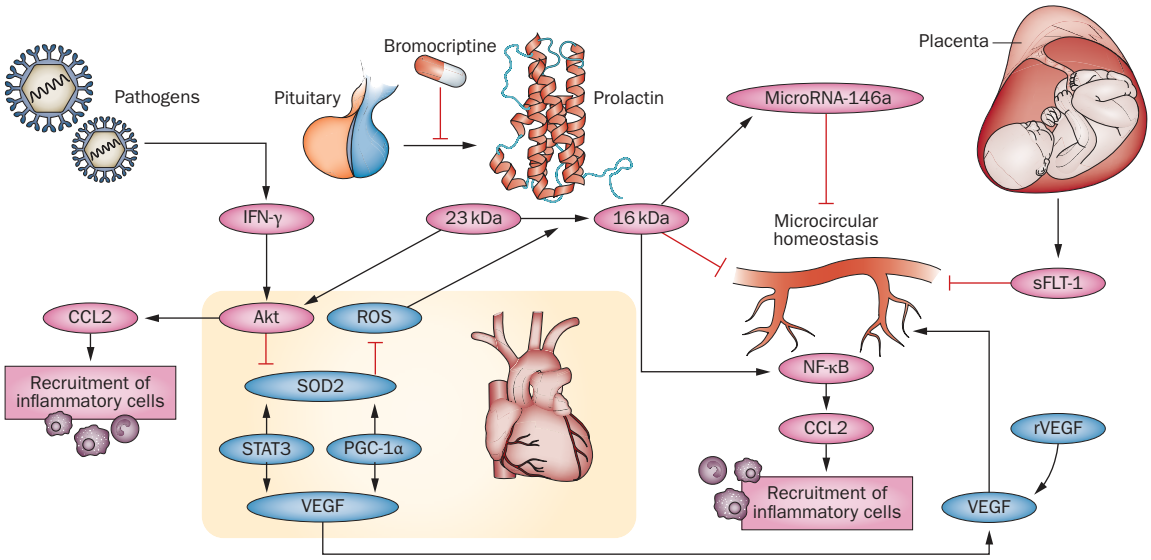

Figure 2 | Pathophysiological mechanisms in PPCM. Prolactin is released from the pituitary gland and, under conditions of oxidative stress in the myocardium, is proteolytically cleaved to a 16 kDa fragment by proteases, such as cathepsin D or matrix metalloproteinases. In PPCM, this process is induced by increased oxidative stress owing to downregulation of the transcription factors STAT3 and PGC-1α and their targets (such as SOD2), or by increased Akt activation, which also suppresses cardiac SOD2 expression. The 16 kDa prolactin leads to increased microRNA-146a expression in endothelial cells, which exerts angiostatic effects and impairs the metabolic activity of cardiomyocytes. The 16 kDa prolactin also enhances CCL2 expression in endothelial cells via NF-κB signalling. Additionally, increased levels of IFN-γ and full-length prolactin promote the upregulation of CCL2 in cardiomyocytes, generating local inflammation in the heart, which is associated with a particularly poor prognosis. STAT3 and PGC-1α are also needed to protect the cardiac vasculature from additional antiangiogenic factors present in the peripartum phase, such as sFLT-1. Both transcription factors increase the cardiac expression of VEGF, which neutralizes the adverse effects of sFLT-1. Blocking prolactin, neutralizing microRNA-146a, or treating with a VEGF agonist might, therefore, be therapeutic options for PPCM. Abbreviations: Akt, RAC-α serine/threonine-protein kinase (also known as protein kinase B); CCL2, C–C motif chemokine 2; NF-κB, nuclear factor NF-κB; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PPCM, peripartum cardiomyopathy; ROS, reactive oxygen species; rVEGF, recombinant vascular endothelial growth factor; sFLT-1, soluble fms-like tyrosine kinase 1 (also known as vascular endothelial growth factor receptor 1); SOD2, mitochondrial superoxide dismutase [Mn]; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor.

partial rescue from PPCM, whereas blocking prolactin with bromocriptine completely prevented the onset of PPCM.[11]

The 16 kDa form of prolactin inhibits angiogenesis at various levels by inducing endothelial cell cycle arrest at the G0–G1 and G2–M stages,[48] in parallel with inhibition of mitogen-activated protein kinase activation induced by basic fibroblast growth factor and VEGF.[49] Additionally, 16 kDa prolactin induces endothelial-cell apoptosis by activating caspase-3 and nuclear factor (NF)-κB,[50] inhibits endothelial-cell migration by downregulating the Ras–Tiam1–Rac1–Pak1 signalling pathway,[51] and attenuates the activation of endothelial nitric oxide synthase, which blocks vasodilatation.[52,53] Finally, 16 kDa prolactin enhances endothelial inflammation by promoting leukocyte adhesion to endothelial cells.[54] The biological effects of 16 kDa prolactin have been extensively reviewed previously.[42] The 16 kDa prolactin is known not to signal via the prolactin receptors, but a receptor of its own has not been identified. However, 16 kDa prolactin activates NF-κB signalling in endothelial cells and thereby upregulates microRNA-146a (miR-146a), which mediates most of the adverse effects of 16 kDa prolactin in endothelial cells.[10] Although 16 kDa prolactin has little direct effect on cardiomyocytes, the molecule induces the release of miR-146a-loaded exosomes from endothelial cells, which enter cardiomyocytes. Exosomal-derived miR-146a downregulates receptor tyrosine-protein kinase erbB-4 in cardiomyocytes and, as a consequence, decreases the metabolic activity of the cells and impairs endothelial-to-cardiomyocyte communication via the neuregulin-1–erbB signalling system.[10] The biological mechanisms by which 16 kDa prolactin affects cardiac cells are summarized in Figure 2.

Evidence suggests that the angiostatic and proapoptotic 16 kDa prolactin might have a causal role in the initiation and progression of PPCM. Suppression of prolactin release using the D_2 dopamine-receptor agonist bromocriptine prevented the onset of disease in several animal models of PPCM (*Stat3*$^{-/-}$, cardiomyocyte-specific *Ppargc1a*$^{-/-}$, and cardiomyocyte-specific overexpression of *Akt1*).[11,12] This notion is supported by initial clinical data from case reports and small studies, which show that the addition of bromocriptine to standard therapy for heart failure is associated with improvement in both left ventricular function and a composite clinical outcome (remaining in NYHA functional class III–IV, failure to improve ejection fraction by >10 absolute units, and death) in women with

acute severe PPCM.[11,34,55–57] However, the combination of bromocriptine and standard therapy for heart failure must be tested in large, multicentre, randomized, controlled trials. We are currently performing such a trial in Germany, where we aim to randomly allocate 60 patients with PPCM to standard therapy for heart failure with or without the addition of bromocriptine.[58]

VEGF signalling and pre-eclampsia

Another antiangiogenic factor that is released in high quantities from the placenta during mid-to-late gestation is sFLT-1. A markedly elevated serum level of sFLT-1 has been associated with pre-eclampsia, a common maternal complication of mid-to-late gestation that affects 3–5% of pregnancies worldwide.[59–61] Clinically, pre-eclampsia causes cardiac dysfunction independently of blood pressure.[59,62] Some reports indicate that pre-eclampsia frequently occurs in patients who subsequently develop PPCM,[7,12,15] and a potential connection between the two diseases has been established. *Ppargc1a*$^{-/-}$ mice develop PPCM that is associated with an increased level of sFlt-1 and insufficient upregulation of cardiac expression of Vegf, a potent proangiogenic factor that is antagonized by sFlt-1.[12] As mentioned above, this model of PPCM also shows compromised protection from oxidative stress and enhanced cleavage of prolactin. PPCM was ameliorated by the addition of recombinant VEGF (rVEGF) or bromocriptine, but full rescue from PPCM was obtained only with the combination of rVEGF and bromocriptine. This result suggests that PPCM might be a 'two-hit' phenomenon. Firstly, systemic antiangiogenic signals occur during late pregnancy (as are present in pre-eclampsia). Secondly, antiangiogenic factors are further upregulated during the peripartum phase, together with host susceptibility in the form of insufficient local proangiogenic defences in the heart.[12]

This model supports the idea that PPCM might start as a disease of the endothelium, leading to loss or damage of the vasculature. As a consequence, functional insufficiency of the heart owing to impaired blood flow is likely. This process might be initiated during pregnancies complicated by pre-eclampsia, in which sFLT-1 is markedly upregulated, and predispose these patients to PPCM. Therefore, therapies that target several antiangiogenic factors in PPCM might be successful. The latest data from a German registry[7] show that the overall rate of both partial and full recovery of patients treated with bromocriptine (96%) is higher than that in other studies, although the rate of full recovery is similar to that in previous studies (summarized previously[63]).

Inflammation

Patients who survive PPCM often tolerate subsequent pregnancies fairly well, particularly if cardiac function has fully recovered.[4,64] However cardiac dysfunction frequently re-emerges in the peripartum and postpartum phases.[4,64] Therefore, the state of pregnancy might be protective even for damaged hearts. On the molecular level, PI3K–Akt signalling is highly activated during pregnancy, partly by increased mechanical stress, but also by high levels of circulating pregnancy hormones, such as oestrogens.[11,65,66] Given that PI3K–Akt signalling is known to promote physiological hypertrophy and cardioprotection, this pathway might, at least partly, be responsible for the adaptation and protection of the maternal heart during pregnancy. After delivery, mechanical stress and oestrogen levels rapidly decrease, and PI3K–Akt signalling is no longer activated.[11] We tested the hypothesis that activating cardiac Akt signalling in the peripartum phase might protect mice predisposed to develop PPCM (the *Stat3*$^{-/-}$ model of PPCM crossed with a cardiomyocyte-restricted, constitutively-active *Akt1* transgene [*Stat3*$^{-/-}$;C*Akt1*^{tg}]).[14] Surprisingly, both C*Akt1*^{tg} and *Stat3*$^{-/-}$;C*Akt1*^{tg} mice developed PPCM with systolic dysfunction.[14] Both genotypes displayed cardiac hypertrophy and reduced capillary density associated with decreased expression of SOD2, enhanced oxidative stress, and an increased level of miR-146a, which indicates increased production of the antiangiogenic 16 kDa prolactin.[14] Additionally, cardiac inflammation and fibrosis were accelerated in *Stat3*$^{-/-}$;C*Akt1*^{tg} mice compared with *Stat3*$^{-/-}$ mice, which was associated with increased postpartum mortality.[14] The prolactin blocker bromocriptine prevented heart failure and the decrease in capillary density in the C*Akt1*^{tg} and *Stat3*$^{-/-}$;C*Akt1*^{tg} mice, which indicates that prolactin has a central role in these two novel models of PPCM.

Subsequent analyses showed that even full-length prolactin might contribute to the pathology of PPCM, because it upregulates the proinflammatory C–C motif chemokine 2 (CCL2).[14] We have previously observed in a cohort of African women with PPCM that increased levels of prolactin and IFN-γ correlated with both a sustained inflammatory state and poor prognosis.[13] In addition to prolactin, IFN-γ also induced CCL2 expression in cardiomyocytes, which was mediated via activation of Akt signalling.[14] These data suggest that the combination of prolactin and a high level of IFN-γ might be detrimental in patients with PPCM. Akt activation might be protective for the maternal heart during pregnancy, but needs to be downregulated in the peripartum phase. Agents that increase Akt activation in the peripartum phase are, therefore, not likely to be appropriate therapies for heart failure in PPCM.

Biomarkers

A diagnosis of PPCM should be considered whenever a woman presents with symptoms of systolic heart failure during the peripartum period. Biomarkers such as an elevated level of N-terminal pro-brain natriuretic peptide (NT-proBNP) are indicative of heart failure in peripartum women.[7] Likewise, an inability to downregulate serum IFN-γ might predict an adverse outcome in patients with PPCM.[13] However, both NT-proBNP and IFN-γ are fairly nonspecific markers for heart failure. Unlike patients with most other forms of cardiomyopathy, those with PPCM have a high likelihood of recovery with adequate therapy. Therefore, risk stratification and management of patients are important to rule out other aetiologies of heart failure, such as underlying DCM or genetic cardiomyopathy.

A direct downstream effector of 16 kDa prolactin, miR-146a, has emerged as a promising potential diagnostic marker to distinguish between PPCM and other cardiomyopathies.[7,10] The observation that miR-146a is released in specific microparticles (endothelial exosomes) from endothelial cells exposed to 16 kDa prolactin is consistent with the discovery that microparticle profiles differ substantially between patients with PPCM and those with DCM.[67] Nevertheless, additional biomarkers are needed to distinguish between PPCM and other types of heart failure, to optimize the diagnosis, management, and risk stratification of these young patients.

Conclusions

Increased awareness of PPCM has benefitted patients with this condition. As clinical data sets are collected and analysed, insight into the pathophysiology of the disease will be improved, providing important information for the diagnosis and management of these patients. A large, international registry of patients with PPCM has been initiated by the ESC via the EURObservational Research Programme.[31] Data from 1,000 patients with PPCM, collected via this programme, will help to improve our understanding of the aetiology, epidemiology, and optimal treatment of this condition.

Experimentally, dysregulation of multiple factors, including STAT3, PGC-1α, and Akt,[11,12,14] in the peripartum heart merge in a common pathway, in which increased oxidative stress and subsequent generation of 16 kDa prolactin impairs the cardiac vasculature and metabolism, finally culminating in systolic heart failure and PPCM (Figure 2). The 16 kDa prolactin pathophysiology seems to be common to patients with PPCM of various aetiologies and from different geographical regions. Moreover, initial evidence suggests that 16 kDa prolactin and its downstream mediators are specific to patients with PPCM, which might allow their use as biomarkers for diagnostic and prognostic purposes in women with peripartum heart failure. Experimental and clinical evidence supports the benefit of bromocriptine in treating women with PPCM, although further data are required from large-scale clinical trials. Activators of Akt signalling seem to be detrimental in PPCM, whereas VEGF agonists and neutralization of miR-146a might be novel therapies for this condition.

Review criteria

A search of the PubMed database was performed using the following terms: "peripartum cardiomyopathy", "preeclampsia", "heart failure", "prolactin", and "preeclampsia and heart failure around pregnancy". The literature cited in this Review derives mainly from the years 2000 to 2014. We selected only full-text, peer-reviewed articles published in English. We searched the reference lists of selected papers for further leads.

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Author contributions

Both authors researched data for the article, contributed substantially to discussion of its content, wrote the manuscript, and reviewed and edited it before submission.