Pathophysiology and risk factors of peripartum cardiomyopathy

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Abstract

Peripartum cardiomyopathy (PPCM) is a potentially fatal form of idiopathic heart failure with varying incidences among countries and races. The cause of PPCM is uncertain but it may result from a combination of environmental and genetic factors, as well as pregnancy associated conditions such as pre-eclampsia. Animal studies suggested that impaired vascular and metabolic function may be central to the development of PPCM. Clarifying the pathogenic mechanisms is necessary to establish new therapies to improve the outcomes of patients with PPCM. Pregnancy hormones tightly coordinate a plethora of maternal adaptive responses, including haemodynamic, vascular, structural, and metabolic changes of the cardiovascular system. While pregnancy is considered to be a cardiovascular challenge, hormonal effects uniquely drive systemic insulin resistance and mostly fatty acid-dependent cardiac metabolism. In PPCM, the peripartum period is associated with profound and rapid hormonal changes that result in a brief period of disrupted cardiovascular (metabolic) homeostasis prone to secondary perturbations. This review summarizes and reflects on recent literature on the potential pathophysiological mechanisms and risk factors for PPCM with a focus on the maternal cardiovascular changes associated with pregnancy. We provide an updated framework to improve understanding of PPCM pathogenesis, which may lead to a better disease definition.

Introduction

Peripartum cardiomyopathy (PPCM) is a form of heart failure associated with pregnancy and the postpartum period[1,2]. PPCM is defined as an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular (LV) systolic dysfunction in the peripartum phase (i.e., towards the end of pregnancy, during delivery or in the months following delivery) where no other cause of heart failure is found[1,3–5]. Diagnosis generally follows the exclusion of other (similar) conditions and differential diagnoses include pre-existing dilated cardiomyopathy, Takotsubo cardiomyopathy,

myocarditis, familial cardiomyopathy and valvular heart disease[1,2,5,6]. Furthermore, outcomes varied greatly in the European Society of Cardiology (ESC) EURObservational Research Programme (EORP) PPCM Registry[4]. Myocardial recovery (i.e., LV ejection fraction [LVEF] >50%) was observed in 46% of patients 6 months after diagnosis and persisting severe LV dysfunction or death was seen in 28% of patients worldwide[4]. Previous studies have indicated that PPCM patients often suffer from hypertension and palpitations, and may have a persisting higher risk for sudden death, arrhythmia, and other cardiovascular complications. Long-term prescribed drug use is common, even in patients with fully recovered LV function[7,8].

PPCM incidence appears to vary markedly among geographical regions, but differing definitions prevent direct comparison of studies. Countries with the lowest reported incidence (i.e., per live birth) include Japan (1 in 16 667)[9,10], Denmark (1 in 10 000)[11], and Sweden (1 in 5882)[12]. In contrast, those with higher rates appear to be Nigeria (1 in 100)[13], Haiti (1 in 333)[14], Pakistan (1 in 840)[15], and South Africa (1 in 1000)[16]. In comparison, estimated incidences in Germany are 1 in 1000 to 1500 live births[17]. Studies in the USA suggest an increasing incidence over the past 20 years[18].

Various pathophysiological mechanisms have been suggested[19–23], but their clinical relevance remains to be confirmed. A common hypothesis states that PPCM is a multifactorial syndrome where several known and unknown factors in the setting of pregnancy may lead to PPCM, i.e., a "multiple-hit model". This hypothesis is supported by the onset of PPCM in mice with a cardiac specific knockout for either the signal transducer and activator of transcription 3 (*Stat3*) gene or the peroxisome proliferator-activated receptor γ coactivator 1α (*Ppargc1a*) gene[19,20]. These mice developed severe heart failure postpartum, but did not present any heart failure-related symptoms before pregnancy[19,20]. A recent study in human induced pluripotent stem cells (hiPSC) derived from patients with PPCM highlighted a role of cardiomyocyte metabolism in the pathogenesis of PPCM[24]. Several pregnancy-associated hormones, including progesterone, oestrogens, prolactin, soluble fms-like tyrosine kinase 1 (sFLT1), and fibroblast growth factor 21 (FGF21) play roles in the coordination of cardiac metabolism[25–27]. Impaired metabolism in PPCM patient-derived cardiomyocytes and

metabolic effects of pregnancy hormones may indicate that the hearts of patients with PPCM cannot cope with the profound fluctuations of hormones and downstream metabolic changes that occur in the peripartum period. This review summarizes and reflects on recent literature on the potential pathophysiological mechanisms and risk factors for PPCM with a focus on the physiological maternal changes associated with pregnancy. We provide an updated framework to improve understanding of PPCM pathogenesis, which may lead to a better disease definition.

Cardiovascular adaptations in pregnancy

PPCM is hypothesized to occur due to the interaction of an external trigger and a predisposition: a "two-hit model". While a putative predisposition remains elusive (but is likely to be genetic), far more is known about the challenges of pregnancy and the effects on the cardiovascular system that could trigger PPCM pathogenesis. Hormones are the key regulatory elements that drive the different stages and related adaptations during and after pregnancy. Maternal adaptations to the cardiovascular system include hemodynamic and structural changes, vascular remodelling, and bioenergetic shifts. These adaptive processes are necessary to prevent diseases like PPCM. Currently, it is unknown which adaptive processes fail in the pathogenesis of PPCM. More research is needed to identify these potentially insufficient mechanisms in PPCM. However, this section provides a basis for such studies by summarizing what is known about physiological pregnancy-related adaptation from a cardiovascular perspective.

Haemodynamic changes

Pregnancy is associated with an increasing blood volume that leads to a chronically elevated cardiac volume load[28]. As a result, cardiac output increases to a prolonged peak from the second trimester to term and corresponds to an increased heart rate by ~20% and stroke volume by ~25%[29–32]. Increases in stroke volume were also found to be higher in subsequent pregnancies compared with

the first pregnancy[29]. Vascular resistance also falls by ~30% in the first trimester and recovers after delivery[29–32]. Gestational blood pressures were previously undefined, but a recent multicentre, longitudinal study in 4,279 women demonstrated that median systolic and diastolic pressures briefly declined during early pregnancy, but rose by 7 mmHg and 9 mmHg, respectively, above nominal pressures by late gestation[32]. These changes appear minor and could explain the inconsistency of previous studies. It is unknown whether haemodynamic changes could lead to PPCM, but low systolic blood pressure and elevated heart rate were associated with worse outcome in patients with PPCM[33].

Structural changes

Parallel to haemodynamic changes, the human maternal heart undergoes substantial remodelling. Both left and right ventricular end diastolic diameters (LVEDD and RVEDD, respectively) increased by ~20%, whereas the left end systolic diameter (LVESD) did not change between the third trimester and postpartum[33]. A meta-analysis of 48 studies indicated that LV mass was about 28% higher in the last trimester of normotensive pregnancy[34]. These observations are indicative of gestational cardiac hypertrophy. Of note, cardiac dimensions and estimated weights were often compared to postpartum time points. While these structural changes are known to be transient, it is unknown whether heart dimensions can fully return to baseline (i.e., pre-pregnant) or the time required to do so. Additionally, several histological studies in rodents have indicated that the extensive cardiac remodelling does not involve fibrosis during or after pregnancy[35–37]. However, similar histological studies have not been performed in healthy women pre- or postpartum as these are limited by the requirement of cardiac biopsies and the associated risks. PPCM can have various cardiac phenotypes including ventricular dilation[1], borderline non-compaction cardiomyopathy[38,39], and peripartum takotsubo cardiomyopathy[40,41], whereas normal pregnancy is associated with reversible eccentric cardiac hypertrophy[42]. This disparity may indicate that regulatory mechanisms involved in physiological cardiac remodelling during and after pregnancy could be impaired, leading to a

decompensated phenotype. Genetic variants of structural genes have been associated with PPCM and are discussed in detail in the *Risk factors* section.

Vascular remodelling

The balance between cardiac hypertrophy and vascular growth is crucial to maintain adequate cardiac function during pregnancy. In concert with increased ventricular mass, the vasculature is required to adapt accordingly. Like fibrosis, data on vascular changes is mostly available from rodent studies. It was shown that capillary density is transiently increased in mice in late pregnancy[19,35]. Specifically, pro-angiogenic gene (including *Vegf*, *Ppargc1a, angiopoietin-1, and Fgf2*) are activated in early and mid-gestation, but return to non-pregnant levels in late gestation[43]. This is in line with the observed antiangiogenic environment associated with late gestation[20]. These findings in rodents corresponded with serum levels of PlGF, which reached a peak in the second trimester as well before returning to baseline levels in the last trimester in humans[44]. In contrast, circulating VEGF appears to be stable in the first two trimesters before increasing near term[45]. Like VEGF, serum levels of soluble VEGF receptor-1 (sFlt-1) were elevated in late pregnancy[46–48]. Since sFlt-1 readily binds circulating VEGF, it is unknown whether the elevated levels of VEGF reflected levels of free VEGF or inactivated VEGF that is bound to sFlt-1. Hence, this may be a physiological response to maintain an angiogenic balance systemically and locally[20]. Disruption of this delicate balance is a key factor in the development of pre-eclampsia and is likely also involved in the pathogenesis of PPCM. Specifically, mice with cardiac ablation of the *Ppargc1a* gene (which encodes the transcription factor PGC-1α) developed a PPCM-like phenotype following inhibition of VEGF signalling[20]. Vascular function and remodelling in the peripartum period are key aspects of PPCM pathophysiology and is discussed in more detail in the following sections.

Maternal cardiac metabolism during pregnancy

The maternal heart undergoes unique bioenergetic changes during pregnancy, which is tightly regulated during each gestational phase. In a normal, non-pregnant, fasted state, the human heart primarily utilizes free fatty acids (FFA) as a source of fuel[49,50]. Other metabolic substrates include ketones, lactate, and amino acids[49,50]. While glucose is one of the principal metabolic substrates for most human tissues, recent studies demonstrated that the heart consumes very little in the average population, at least in the fasting state[49,50]. As pregnancy progresses, maternal metabolism shifts from a predominant anabolic state with increased fat stores to a catabolic state with reduced fat mass and elevated levels of circulating FFA to meet the energetic needs of the foetus[51]. The transition from an anabolic state to a catabolic state is characterized by a profound increase of basal metabolic rates in mothers by up to 60%[52]. Insulin signalling plays a pivotal role in coordinating this shift. Insulin resistance gradually develops with gestation and results in hyperglycaemia and hyperinsulinemia in late pregnancy[53,54]. Consequently, glucose uptake is limited in the maternal body and is shunted to the foetus. Little is known about how cardiac metabolism changes during pregnancy in humans, but animal studies have provided insight into the associated molecular mechanisms. Early studies in rats showed a reduction in cardiac glucose oxidation by ~75% during pregnancy[55], and studies in dogs indicated similar suppression of glucose use and a near doubling of FFA oxidation during late pregnancy[56]. Despite this metabolic shift towards FFA oxidation, and in contrast to insulin resistance in the liver and skeletal muscle, the hearts of mice in late pregnancy retain insulin sensitivity (defined as activation of signalling cascade)[57]. The causes for these metabolic changes is incompletely understood, but likely include inhibition of glycolysis by high levels of FFA in late pregnancy according to the Randle cycle[58], and specific cellular reprogramming through hormonal signalling, such as induction by progesterone of PDK4, an endogenous inhibitor of PDH and thus of carbohydrate use (**Figure 1**)[59]. Understanding how cardiac bioenergetics are regulated is crucial to understanding the underlying mechanisms of heart diseases in general. Deletion of PGC-1α resulted in angiogenic imbalance, but PGC1α is also a key regulator of major metabolic pathways, especially related to fatty acid oxidation[20]. *In vitro* studies have also indicated

that PPCM patient-derived cardiomyocytes demonstrated reduced viability and metabolic flexibility upon inhibition of lipid metabolism[24]. Hence, impaired metabolic regulation may be a central aspect of the development of PPCM.

Cardiovascular effects of hormones

Sex and pregnancy-related hormones are the key modulators of the various stages of pregnancy. Several hormones are known to profoundly affect the cardiovascular system, but their specific molecular mechanisms and pathways are largely unknown. A plethora of association studies are available on hormone levels and effects regarding the pregnancy and foetal status, but most cardiovascular mechanisms have been demonstrated in animal models (**Figure 2**).

Oestrogens are a class of sex hormones that govern the development of the female reproductive system as well as pregnancy. Oestrogen levels increase progressively during pregnancy and instantly decrease after delivery[60]. Cardiovascular effects of oestrogens are pleiotropic and exert mainly cardiovascular protective effects[61]. Oestrogens induce angiogenesis and vasodilation through increased NO synthesis[62,63] and secretion of VEGF and PlGF[64,65]. Additionally, oestrogens were found to reduce inflammatory signalling, attenuate cardiac hypertrophy, and are protective against oxidative stress in endothelial cells and cardiomyocytes[66–68]. Many of its protective effects are derived from the potent inhibition of apoptosis in cardiomyocytes and endothelial cells[69,70]. It was recently demonstrated that a related class of receptors, the oestrogen-related receptors (ERRs), widely regulate cardiac metabolism, contractility, and conduction properties[71].

Like oestrogens, progesterone is primarily produced by the placenta during pregnancy with increasing serum levels toward delivery. Progesterone was shown to protect against apoptosis by direct inhibition of the L-type voltage dependent Ca2+ channel (in dogs) and via induction of the BCL2 Like 1 gene (*Bcl2l1*; in mice)[72,73]. Furthermore, eNOS mediated NO synthesis is enhanced after progesterone stimulation in the endothelium, causing a marked reduction in vascular resistance in pregnant rats and humans[74,75]. Recent studies in animals have demonstrated that progesterone can

inhibit glycolysis via Forkhead box protein O1 (FOXO1)-mediated mechanisms in tumors[76,77]. In cardiomyocytes, progesterone induced pyruvate dehydrogenase kinase (PDK4) activity, which inhibits pyruvate dehydrogenase, an essential step in glycolysis[57].

Prolactin has been widely associated with PPCM pathogenesis and is discussed in detail in the section on *Pathophysiology*. Serum levels peak at term and rapidly fall to pre-pregnancy levels after delivery if it is not repeatedly stimulated by breastfeeding[78]. Cardiovascular effects of prolactin include a blunted response to angiotensin in rats[79], endothelial pro-survival signalling via the Janus activator kinase (JAK)-signal transducer and activator of transcription (STAT) signalling pathway[80], and reversed phenylephrine-induced vascular tone in rat aortic rings[81]. Clearly such potential effects of prolactin are dose-related, and high dosages/concentrations often used in those studies preclude firm conclusions on the role of prolactin in humans.

A lesser-known pregnancy-related hormone is FGF21, which is mainly produced by the liver during pregnancy under the control of PPAR-α[82–84]. The vast majority of studies were done in animals, as reflected in the following section. In addition, the heart is a target and a source of FGF21[85]. Downstream effects of FGF21 signalling in the heart are related to protection against pathological hypertrophy and damage following myocardial infarction[85,86]. Remarkably, cardiac remodelling was absent in pregnant FGF21 knockout mice and FFA oxidation was significantly reduced[26]. Most of these mechanisms remain to be confirmed in humans, but FGF21 has been correlated to maternal body mass index and adiposity[87]. Moreover, fasting glucose levels also inversely correlated with FGF21, which may reflect maternal nutrient status in pregnancy[87]. By extension, FGF21 has also been suggested as a biomarker for gestational diabetes mellitus and type 2 diabetes mellitus[88].

Biomarkers and risk factors

This section briefly discusses biomarkers that support the diagnosis of PPCM and could result from underlying disease mechanisms. Furthermore, while the cause of PPCM is currently unknown, several risk factors have been proposed, including heart failure-associated genetic defects[89],

ethnicity[4,90], hypertensive disorders[91], infections[92], twin and subsequent pregnancies[93], and previous cancer[94].

Biomarkers

Several studies have determined whether specific biomarkers were associated with PPCM, which were summarized by Cherubin et al[95]. The authors evaluated 117 biomarkers from 31 case-control studies. Several biomarkers were identified as be independent risk factors for PPCM. See **Table 1** for an overview of biomarkers. A quantitative meta-analysis suggested that patients with PPCM had higher levels of natriuretic peptides, troponin, CRP, and white blood cell counts, but reduced levels of albumin and selenium compared with healthy controls[95]. Note that these biomarkers mostly reflect the presence of cardiomyopathy and appear to be unspecific for PPCM. However, a few studies investigated potential PPCM-specific biomarkers by comparing patients with PPCM to patients with other types of heart disease. Increased levels of prolactin[96], miR-146a[21,97], and PlGF[48] were found in patients with PPCM relative to non-pregnancy-related heart failure. Additionally, the ratio between circulating sFlt-1 levels and PlGF was suggested to have significant diagnostic value for PPCM[48]. Identifying more PPCM-specific biomarkers is a great unmet need and will significantly improve diagnosis and prognosis as targeted treatments can be started sooner.

Table 1 – Biomarkers as risk factors for PPCM.

Biomarker	Odds Ratio	95% confidence interval
B1R and M2R[98]	18.786	1.926 – 183.262
antimyocardial IgG[99]	2.68	1.19 – 4.85
NT-proBNP[100]	1.92	1.12 – 4.15
CRP[99,100]	1.86	1.08-4.02
Uric acid[101]	1.3	1.049 – 1.614
ACE polymorphism[102]	0.253	0.114 – 0.558

B1R: Bradykinin B1 receptor, M2R: M2 muscarinic receptor, IgG: Immunoglobulin G, NT-proBNP: N-terminal pro b-type natriuretic peptide, CRP: C-reactive, ACE: angiotensin converting enzyme.

Genetics

As PPCM and dilated cardiomyopathy (DCM) have similar clinical characteristics, and it may be that PPCM is part of the spectrum of DCM. Some patients diagnosed with PPCM may have had a previously unrecognised dilated cardiomyopathy, although in the few documented cases where echocardiography was incidentally available prior to clinical diagnosis of PPCM, ejection fraction was normal[103]. Recent studies indicated that genetic variants of in Titin (*TTN*)[89,104–107], cardiac Troponin C (*TNNC1*)[108], Desmoplakin (*DSP*)[89,107], Lamin A/C (*LMNA*)[89,107], BAG Cochaperone 3 (*BAG3*)[89,107], Filamin C (*FLNC*), Myosin Heavy Chain 6 and 7 (*MYH6* and *MYH7*)[89], and Vinculin (VCL)[89,107] were identified in both PPCM and DCM. Truncating variants of *TTN* were found in 10% of patients with PPCM. Mutations in *DSP*, *FLNC*, and *BAG3* which were previously associated with DCM have now also been confirmed in PPCM patients[89,106,107]. in addition, the frequencies with which mutations in each of these genes are found in patients with PPCM closely mirrors the same frequencies in patients with DCM, underscoring the similarity of genetic predispositions to both diseases. The association of *BAG3* variants and PPCM has also prompted the hypothesis that various classes of molecular chaperones (e.g., heat-shock proteins) could be involved in the pathogenesis of PPCM[109]. A small genome wide association study identified enrichment of a single nucleotide polymorphism near the Parathyroid Hormone Like Hormone (*PTHLH*) gene in 79 PPCM patients, although this observation requires confirmation[110]. PPCM and DCM may be caused by similar gene variants, of which *TTN* mutations seem to be most prevalent. However, how these various mutations converge and lead to PPCM remains to be investigated.

Geographical variation

Very little is known about the geographical variation on PPCM, despite global initiatives like the ESC EORP. Most studies did not select patients using consecutive screening (i.e., patients were selected based on PPCM diagnosis) and too few countries were affiliated with these studies. Ideally, a registry could be started that includes patients based on consecutive screening (e.g., include all pregnant women and note incidence of PPCM) and is performed consistently in as many countries as possible.

However, this is an ambitious endeavour that is has not been initiated yet and conclusive data on incidence rates remains limited by regional studies. Consequently, this section summarizes what is known from local studies (with non-consecutive screening) and indicates which factors could be considered if a global registry is initiated with consecutive patient inclusion.

Recent studies demonstrated that the incidence of PPCM varies among geographical regions, with the lowest reported rates in several European and Asian countries[10]. PPCM incidence is highest in Nigeria and Haiti[13,14,111]. These geographical hotspots support the hypothesis that a specific genetic background may underlie the disease although environmental factors are also likely. The recently concluded PEACE registry in Nigeria was a national consecutive study and indicated that selenium deficiency and malnutrition were significantly associated with PPCM[111,112] and selenium supplementation could be beneficial in the treatment of PPCM[113]. Micronutrient deficiency and malnutrition in general are examples environmental factors that could predispose to heart failure[114] and could trigger PPCM. Selenium deficiency is also common in neighbouring regions of Nigeria and in the Keshan region in China, but PPCM incidence rates are unknown for these regions. In contrast, studies from the USA that encompass a diverse population within the same healthcare system corroborate that race is an important risk factor. Multiple nationwide studies from the USA have demonstrated that over 40% of patients were African-American and 35% were Caucasian[18,90,115,116], in contrast to population estimates of 60.3% non-Hispanic Caucasian and 13.4% African American[117]. Two independent US studies demonstrated fundamental differences between Caucasian and African American patients, as African American patients were younger, had a higher prevalence of gestational hypertension, had a lower LVEF at diagnosis, and functional recovery was less likely or more slowly in African American patients compared with Caucasians[118,119].

Socio-economic status

Since the ESC EORP is a global study, healthcare systems differ among included countries which may skew the results. An interim report of the ESC EORP indicated that patients from countries with

middle to high health expenditure were 64.6% Caucasian compared with 5.1% Black[120]. However, patients from countries with a predominantly low health expenditure were Black or Asian (45.2% and 39.4% respectively)[120]. In this regard, low socio-economic status (specifically lower education) was associated with worse outcomes independent of race[121]. Despite marked differences in socio-economic background, the mode of presentation was largely similar. Isogai et al. compared PPCM incidence with all-cause maternal mortality per country and found a significant correlation (Spearman correlation: 0.80)[10]. PPCM is a major cause for maternal death and likely drives such increased maternal mortality rates. In general, maternal mortality rates are relatively high in low-income countries due to suboptimal treatment regimens and low hospitalization rates. Additionally, birth rates are lower for high-income countries versus low-income countries. Suboptimal healthcare (i.e., lack of genetic screening), more subsequent pregnancies, and a lack of contraception and family planning may indirectly contribute to the high incidence of PPCM in specific regions[122,123].

Pre-eclampsia and vascular dysfunction

Pregnancy-associated hypertension and its more severe form pre-eclampsia, and PPCM are both cardiovascular diseases that can affect women during late-gestation. Pre-eclampsia is defined as new-onset hypertension and proteinuria or new-onset hypertension with end-organ dysfunction with or without proteinuria after 20 weeks of gestation. The exact relationship between PPCM and pre-eclampsia is not fully understood, but pre-eclampsia strongly predisposes to PPCM[124,125]. Whether the increased cardiovascular risk is due to direct consequences of the underlying cause of pre-eclampsia or due to shared risk factors is currently unknown[91,126,127]. A substudy of the ESC EORP described the differences in phenotypes and outcomes of PPCM patients with and without hypertensive disorders, including pre-eclampsia[91]. Patients with PPCM and pre-eclampsia presented with worse symptoms, but the LVEF of women with both diseases was more likely to recover than in PPCM patients without hypertension[91]. Patients with PPCM and pre-eclampsia were more likely to have peripheral oedema, pulmonary rales, a high body mass index (BMI), short QRS durations, and

New York Heart Association (NYHA) class IV symptoms[91]. One reason for improved outcomes in patients with PPCM and pre-eclampsia may be that these patients are diagnosed and treated earlier in disease progression[128].

Pre-eclampsia is in part caused by impaired placental function resulting in excessive levels of circulating angiostatic factors such as sFlt-1 and placental growth factor (PlGF) secreted by the placenta[46,129]. An excess of sFlt-1 was shown to inhibit vascular endothelial growth factor (VEGF)-induced vasodilation, reduce capillary density, and cause endothelial dysfunction[20,46,130]. Similarly, increased levels of sFlt-1 and 16kDa prolactin were also associated with PPCM patients[20,131]. Mouse models for PPCM have indicated that the levels of 16kDa prolactin induced similar vascular dysfunction[19,20]. However, this mechanism remains to be confirmed in humans.

Immune responses

PPCM is also associated with specific immune responses (possibly following viral infections[132]) that may increase susceptibility or result in worse outcomes. Serum markers related to inflammation (i.e., C-reactive protein [CRP], tumor necrosis factor-alpha [TNF-α], and interleukin 6 [IL-6]) were significantly increased in PPCM patients compared with controls[133]. A recent substudy of the IPAC study determined that IL-22 and TNF-α were associated with adverse outcome and IL-22 and IL-17 corresponded with disease severity, whereas IL-2 and IL-4 correlated with recovered LVEF at 12 months postpartum[134]. Circulating NK cells were reduced while specific subsets of T cells were increased early postpartum in PPCM patients versus pregnancy matched controls[135]. Recovery of immune cell levels was generally quick, but recovery of NK cells was delayed particularly in black women[135]. Additionally, autoantibodies against troponin I or cardiac sarcomeric myosin were also found in patients and correlated with lower LVEF and reduced cardiac recovery at follow-up[136]. Notably, the cause for (auto)immune responses can be variable and remains to be specified.

Subsequent pregnancies

Subsequent pregnancies pose an increased risk for recurrence or worsening of heart failure in patients with PPCM[137,138]. Unrecovered left ventricular function at the time of a subsequent pregnancy was associated with a higher risk of a fatal outcome regardless of age, gravidity, parity, hypertension, and smoking[138]. Study parameters varied among studies, but the consensus is that all subsequent pregnancies were associated with significantly reduced LVEF regardless of LVEF recovery after the index pregnancy[138,139]. Mortality following the subsequent pregnancy was significantly higher in women with persistently impaired LVEF (<50%) compared with women with recovered LVEF[138,139]. Therefore, PPCM could result in persisting subclinical cardiac dysfunction and subsequent pregnancies may aggravate cardiac function recurrently. It is not clear to which extent this deterioration continues, but is likely that cardiac function will decline continuously with each subsequent pregnancy[140,141].

Cancer

The prevalence of cancer was also indicated to be 16-fold higher in PPCM patients compared to age-matched women[94]. 57% of patients were diagnosed with cancer prior to PPCM presentation of which 92% were treated with cardiotoxic cancer therapies, which likely contributed to deterioration of LV function when PPCM developed and delayed full cardiac recovery therafter[94]. Whole exome sequencing revealed that 6 out of 14 screened patients carried potential pathogenic gene variants associated with cardiomyopathy or cancer predisposition syndromes[94]. However, in a large South African PPCM cohort there was no association of cancer diagnoses with PPCM diagnosis (unpublished data). Thus, it is not yet clear whether screening for genetic variants and for cancer in PPCM patients is warranted.

Pathophysiology

Very little is known about the pathophysiology of PPCM in humans. The previously described risk factors provide some insight into the state of patients with PPCM at the time of diagnosis and at different times of follow up, but these data do not support inference regarding pathological mechanisms that eventually precipitate into PPCM. Most mechanistic data were obtained from animal models that presented a phenotype that is similar to PPCM in humans. While these models helped shape some of the clinical guidelines and pathogenic hypotheses, most putative mechanisms remain to be confirmed in humans.

Mouse models for PPCM

The two main mouse models used to study PPCM were based on cardiac-specific deletion of the *Stat3* or *Ppargc1a* gene[19,20]. Mice with either genotype developed severe heart failure postpartum that closely resembled PPCM with increasing severity in subsequent pregnancies[19,20]. Abrogation of STAT3 or PGC-1α-mediated signalling pathways resulted in an impaired response to oxidative stress related to late pregnancy and early postpartum[19,20,142]. The PI3K-Akt pathway is thought to be cardioprotective during, but transgenic overexpression of Akt in concert with *Stat3* knockout could not prevent the onset of PPCM[143]. Consequently, stressed cardiomyocytes secreted the ubiquitous lysosomal protease cathepsin D following hypoxic stress, mechanical stretch, and oxidative stress in addition to regulated exocytosis[19,144,145]. Extracellular cathepsin D exhibited proteolytic cleavage of the nursing hormone prolactin during the peripartum period[19,146,147]. The produced fragment is a peptide known as 16 kDa prolactin and is classified as a vasoinhibin and part of a family of peptides that elicit antiangiogenic effects[148]. Subsequently, the 16 kDa prolactin fragment interacted with the urokinase plasminogen activator surface receptor (uPAR) on the cell membrane of adjacent endothelial cells and endocytosis was induced by circulating plasminogen activator inhibitor-1 (PAI-1)[21,23,149]. This mechanism effectively inhibited migration and cell cycle progression, and induced apoptosis in endothelial cells, subsequently disrupting the cardiac microvasculature[150–152]. Consequently, endothelial cells secreted exosomes loaded with microRNA-146a (miR-146a), which

were taken up by surrounding cardiomyocytes[21]. MiR1-146a effectively decreased protein levels of Erb-B2 Receptor Tyrosine Kinase 4 (ERBB4) and neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) in cardiomyocytes[21,153]. The effects on NRAS-mediated mechanisms were minimal as NRAS expression is low in cardiomyocytes. In contrast, ERBB4 mediates cardiac development and metabolic processes, but its role in PPCM pathogenesis remain undefined[154,155]. In addition, PGC-1α regulates the expression and production of VEGF and, therefore, facilitates angiogenesis. This pathway likely offsets the antiangiogenic effects of high sFlt-1 levels at term and cardiac deletion of PGC-1α predisposes mice to cardiomyopathy even in the absence of pregnancy[20,156]. Thus, impaired STAT3 and PGC-1α-mediated mechanisms resulted in striking PPCM phenotypes in mice via an induced angiogenic imbalance and abnormal metabolic regulation. See **Figure 3** for a summary of these molecular mechanisms.

Translating pathophysiology from mice to humans

The previous section focused on the potential pathogenic pathways leading to PPCM in mouse models, but these mechanisms remain to be confirmed in humans. Results from these mouse models provided a strong basis for clinical trials of bromocriptine to study the inhibition of prolactin release in PPCM patients, which showed promising outcomes[157,158]. Bromocriptine is a dopamine agonist that supresses prolactin release from the pituitary gland and was hypothesized to ameliorate the adverse effects of 16 kDa prolactin. However, translating the findings from mice to the human situation has proven difficult as several caveats exist. For example, the mouse models were based on cardiac-specific deletion of *Stat3* and *Ppargc1a*, which is not representative for PPCM patients. However, STAT3 is a main regulator of inflammation and STAT3 activation and protein levels were greatly reduced in hearts of patients with dilated cardiomyopathy or PPCM, which suggests that STAT3 is essential to mount an adequate response upon cardiac stress[19,159]. One study also showed that circulating prolactin levels were elevated in PPCM patients versus pregnancy-matched control while both groups were nursing[96], but these results remain to be replicated. A study in a German

cohort demonstrated that serum levels of cathepsin D and miR-146a were also significantly elevated in PPCM patients[97]. Normal levels of circulating miR-146a were observed in all PPCM patients who had already received early bromocriptine treatment[97]. Additionally, the antiangiogenic effects of 16 kDa prolactin is central to the proposed pathophysiology and increased circulating levels have been shown in a few PPCM patients[19]. Due to the lack of quantitative assays for vasoinhibins, no reference ranges or serum levels in disease have been determined. While prolactin, cathepsin D, and miR-146a were shown to be elevated in PPCM, the role of 16 kDa prolactin remains a topic of debate since cathepsin D produces five distinct vasoinhibins of which four are potent antiangiogenic agents and should be investigated further[147,160]. Moreover, human prolactin is not readily cleaved by cathepsin D in most extracellular conditions, mostly dependent on pH[161,162].

Extrapolations from animal models may be difficult regarding the specific role of prolactin, but the notion of angiogenic imbalance in PPCM pathophysiology remains promising[163]. The systemic antiangiogenic state during late pregnancy and early postpartum is negated by local VEGF production in the hearts of mice[20]. The effects of excessive levels of sFlt-1 were significantly associated with vascular dysfunction and pre-eclampsia in humans[130], which supports the hypothesis that PPCM may be a predominantly vascular disease of the heart. While angiogenic therapies were beneficial in pre-eclamptic rats and PPCM mouse models, clinical studies cannot be conducted yet as human pregnancies take much longer and trials will be complicated by vast interindividual differences[20,164]. PPCM onset is generally later than pre-eclampsia, but angiogenic imbalance may be pivotal in both diseases. Serum levels of sFlt-1, PlGF, and the sFlt-1/PlGF ratio are used to diagnose pre-eclampsia and may also be used in the diagnosis of PPCM[47,48]. Therefore, from a vascular perspective, PPCM and pre-eclampsia may be part of a spectrum of cardiovascular diseases associated with a vascular dysfunction.

Metabolic contribution to PPCM

Pregnancy has evolved as a tightly regulated process with major consequences for both the mother and child when certain aspects are disrupted. Insight into specific aberrant metabolic pathways in PPCM patients is scarce. Specific genetic factors have recently been associated with PPCM recently and it is hypothesized that an underlying (genetic) factor may cause cardiovascular distress that results in PPCM. A recent study examined the differences between hiPSC-derived cardiomyocytes from typical PPCM patients and their respective familial controls[24]. To mimic pregnancy-related cardiac volume overload, cyclic mechanical stretch was applied to cultured cardiomyocytes. While mechanical stretch caused differential expression of 2647 genes, of which 1248 specific to the PPCM cardiomyocytes, computational pathway analysis was ambiguous. This suggested that mechanical stretch did not elicit pathological effects in PPCM cardiomyocytes. In contrast, 95 genes were differentially expressed in all stretched cardiomyocytes and in static PPCM cardiomyocytes, but not static cardiomyocytes derived from controls. The majority of enriched pathways was found to be related to lipid metabolism. Cardiac lipid metabolism is known to be reduced during cardiac stress and disease[49,50,165]. However, aberrant pathways related to lipid metabolism in static PPCM cardiomyocytes indicated a specific predisposition that was also functionally confirmed in vitro in these hiPSC-derived cardiomyocytes and in isolated cardiomyocytes from cardiac specific STAT3 knockout mice. Further analysis indicated that the majority of differentially expressed genes are controlled by several shared transcription factors, including nuclear transcription factor Y (NFY), Sp1 transcription factor (SP1), and sterol regulatory element-binding transcription factor 1 (SREBP1). Considering these experimental results, there might be a link between unstable metabolism and endocrine regulation of cardiac metabolism during pregnancy. Most PPCM patients had no indication of cardiovascular disease prior to the onset of PPCM. Moreover, mutations in the *TTN* gene may result in metabolic abnormalities as well. Truncating variants of *TTN* mutations have been associated with PPCM[89,106,166] and were shown to have pleiotropically detrimental to cardiac function[167]. A recent study compared cardiomyopathy patients with and without truncating *TTN* variants and showed that these TTN variants were associated with cardiac fibrosis and mitochondrial

dysfunction[168]. Various were enriched based on genome-wide transcriptome analysis in patients with truncating TTN variants versus patients without, including oxidative phosphorylation, carbon metabolism, pyruvate metabolism, glycolysis, and PPAR signalling[168]. Additionally, mutations in the sarcomeric proteins troponin T and C have been shown to modify the calcium binding affinity during contraction, which resulted altered ATP consumption and increased energetic demands[169,170]. Destabilizing mutations in the *MYH7* gene were shown to have detrimental effects on cardiac function as well, but specifically on metabolic remodelling, glycolysis, and overall mitochondrial function[171]. It is unknown how these sarcomeric alterations might induce PPCM, but they could be considered to predispose to the disease. Pregnancy gradually introduces various cardiovascular stresses. The steady increase of stress might be slow enough for the cardiovascular system to cope with these changes, but perhaps the sudden reversal of most pregnancy-related changes after delivery presents an overwhelming challenge. In contrast, the conditions of late pregnancy may present a specific challenge in itself, which might explain the onset of PPCM during the last trimester. For example, high levels of progesterone and FGF21 could disrupt the metabolic balance in heart, leading to cardiac distress[26,57]. Fluctuations of prolactin-derived vasoinhibins might impair the delicate angiogenic balance as well, leading to impaired vascular function that may be mediated through miR-146a[20,21]. Since vascular function is related to the supply of metabolic substrates and hypoxia, this could induce cardiac metabolic stress as well[172].

Translational opportunities and future studies

The majority of studies pertaining to PPCM resulted in correlations of clinical characteristics and biomarkers. A great unmet need remains to determine how these correlations are related to the underlying pathophysiology of PPCM. Since pregnancy is a defining aspect of PPCM, future studies will be limited to an *in vivo* design. However, it is very difficult to develop a representative animal model for a putative “multiple-hit” disease; especially PPCM considering the variety of risk factors. Determining pathological genetic factors are also limited by a varying disease definition among

countries, which will dictate the nature of patients included in cohort studies. This will be a dynamic and adaptive process before a definitive disease definition can be reached. However, studies performed by Mizuno et al. and Murashige et al. determined which metabolic substrates are used in the heart in a healthy and a diseased state[49,50]. Such studies could be repeated in PPCM patients at the time of diagnosis, and analyses could be expanded beyond metabolomics to also include (targeted) proteomics to determine hormone levels and levels of other endocrine factors. This could be repeated during and after recovery of PPCM in order to elucidate the changes in molecular circulating profiles. Such studies would be mildly invasive and will likely be limited to postpartum PPCM patients. Additionally, since cardiac biopsies are often unobtainable, molecular mechanisms could be studied in other tissues instead, like in the skeletal muscle. While significantly different in various respects, some essential pathways are shared among skeletal tissues and could provide valuable information. Further genetic screening can be done to discover genetic variants in coding and non-coding genes. Currently, such studies are hampered by high costs, sample availability, technological, and statistical limitations. Several genetic variations have been associated with PPCM, but the combination of genetic variation differs among individuals, number of identified genes, and scarcity of PPCM patients greatly limits the statistical power to improve genetic screening at this time. Once a potential pathological factor has been identified, animal models could be developed depending on the nature of that factor. For example, some animal models are more suitable for epigenetic studies, pregnancy studies, or hormone homology. Importantly, most molecular aspects of pregnancy are conserved in placental mammals, but duration and placentation differs greatly among species. Mouse models may be unsuitable to study analogous mechanisms from human and animals with a longer gestation would be required.

Conclusions

PPCM is a complex disease with many risk factors and hypothesized aetiologies. Clear guidelines have been proposed and are regularly updated to reflect novel insights and observations.[1] Since the

pathogenesis of PPCM is still largely unconfirmed in humans, diagnosis is difficult and targeted screening is advised to be started early upon suspicion of PPCM. Extensive cohort studies like the ESC EORP are crucial to gain a better understanding of the clinical presentation, risk factors, and prognosis,[4] but a registry on a global scale with consecutive patient selection will be highly incremental to our knowledge regarding geographical variation and incidence rates among countries. Moreover, recent insights into associated genetic factors and predisposition to PPCM indicated that these may predict a worse prognosis and have relevant clinical implications. Genetic evaluation may, therefore, be advisable for patients with a family history of cardiomyopathies. Moreover, little is known about the relationship between PPCM and pre-eclampsia. Disease definitions suggest that the diseases are fundamentally different, but the initial clinical symptoms may be indicative for both and have historically been a reason for a delayed diagnosis. However, while high blood pressure is required for pre-eclampsia, it is not for PPCM, which is characterized by a significant decline in LV function. Typically, PPCM occurs in the first months after delivery, whereas pre-eclampsia is seen in the second half of gestation and is effectively treated by removing the placenta. Pre-eclampsia may be a distinct entity, but it was repeatedly shown to be a risk factor to develop PPCM, which may suggest that pre-eclampsia may cause lasting damage to the maternal vasculature. The cardiovascular system undergoes fundamentally different changes in late pregnancy compared with the early postpartum period and the underlying cause for PPCM may be related to each period or the transition caused by delivery. From a mechanistic perspective, PPCM appears to result in heart failure secondary to vascular dysfunction. The two principal mouse models have demonstrated that regulation of angiogenesis during the peripartum period is tightly regulated and remarkably sensitive to detrimental stimuli[19,20]. Currently, these animal models are the basis for several clinical studies and clinical recommendations, despite the uncertainty of how well findings in animals can be extrapolated to human patients. Hence, there is a great need for mechanistic studies in humans with PPCM in order to gain more insight into the pathophysiology of PPCM. In light of this, it was recently shown that hiPSC-derived cardiomyocytes from PPCM patients were

538 metabolically impaired *in vitro*[24]. Pregnancy hormones extensively orchestrate maternal metabolism
539 and angiogenesis during and after pregnancy. Alternatively, mutations in several genes have been
540 associated with PPCM, some of which may also cause metabolic distress. However, it is unclear how
541 these dysfunctional gene variants could interact with the mechanisms of pregnancy at specific times.
542 It is known that placental hormones can cause pre-eclampsia; it remains unclear if a specific
543 hormone profile can be distinctly linked to PPCM pathogenesis. Taken together, pregnancy
544 hormones might link the delicately balanced angiogenic state to potentially unstable metabolic
545 processes in the heart of PPCM patients.

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Figure legends

Figure 1 – Pregnancy hormone levels correlated to the cardiac bioenergetic profile. Fluctuating hormone levels correlate with changes in cardiac metabolic substrate during the progression of pregnancy. Late gestation is associated with increased utilization of free fatty acids and ketones, while pyruvate and lactate usage is reduced. The yellow line denotes childbirth and red gradients highlight general time of PPCM onset.

Figure 2 – Pregnancy hormones elicit tissue-specific effects. The pregnancy hormones prolactin (and its cleavage product 16 kDa prolactin), oestrogens, FGF21, and progesterone have pleiotropic effects in the vasculature and in cardiomyocytes related to apoptosis, angiogenesis, metabolism, vascular function, cardiac hypertrophy, and oxidative stress.

Figure 3 – hypothesized pathogenic pathways of PPCM. During early gestation, the placenta secretes high levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) into the maternal circulation, which stimulate vascularization and organ perfusion. As pregnancy progresses, circulating levels of VEGF and PlGF rise in concert with the increased secretion of the angiostatic soluble VEGF receptor-1 (sFlt-1). Alternatively, cardiomyocyte stress induces the exocytosis of the proteolytic enzyme cathepsin D (CTSD), which cleaves prolactin into 16 kDa fragment that is cytotoxic to endothelial cells. Consequently, endothelial cells secrete exosomes loaded with microRNA-146a (miR-146a) and inhibits various cardiomyocyte processes, including ERBB4-mediated metabolism. Both mechanisms have a central role for the vasculature in the heart and may lead to the development of PPCM.

Key points

1. Physiological cardiovascular changes during pregnancy appear to uniquely boost PPCM development in predisposed women.
2. PPCM onset typically overlaps with the most profound changes in hormone levels.
3. Models for PPCM indicate disruption of metabolic flexibility and angiogenic balance, possibly due to aberrant hormonal signaling.
4. Most mechanisms derived from animal models remain to be confirmed in humans but form the basis for current clinical guidelines and future experiments.
5. Registries should be based on consecutive screening and help to determine actual geographic variation of incidence rates.

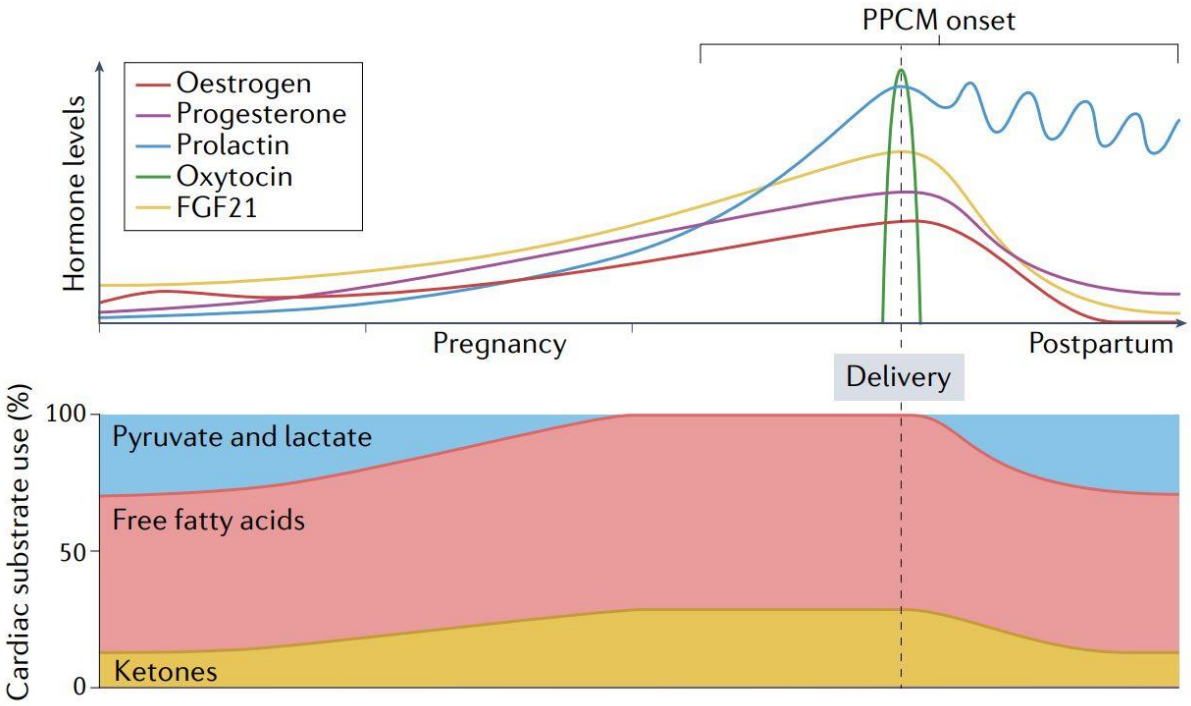
Competing interests

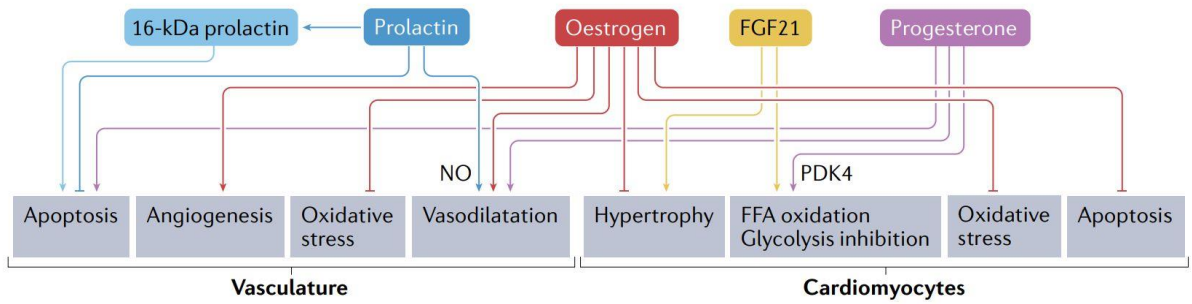
J.B. received honoraria for lectures/consulting from Novartis, Vifor, Bayer, Servier, Abiomed, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, Daichii Sankyo, CVRx, BMS, MSD, Amgen, Corvia, not

related to this article; and research support for the department from Zoll, CVRx, Vifor, Abiomed, not related to this article. P.v.d.M. received consultancy fees and/or grants from Novartis, Corvidia, Singulex, Servier, Vifor Pharma, Astra Zeneca, Pfizer, Pharmacosmos, PharmaNord and Ionis.

Author contributions

M.F.H. wrote the manuscript. All authors contributed substantially to the discussion of content, researching data for the article, and editing before submission.


PPCM onset
Hormone levels
Oestrogen
Progesterone
Prolactin
Oxytocin
FGF21
Pregnancy
Delivery
Postpartum
Cardiac substrate use (%)
100
50
0
Pyruvate and lactate
Free fatty acids
Ketones


16-kDa prolactin
Prolactin
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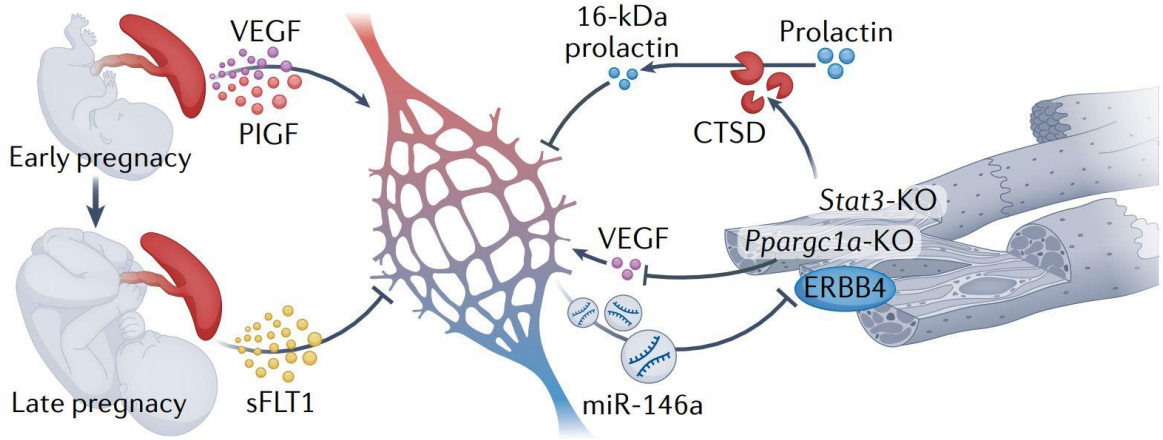
VEGF
PIGF
Early pregnacy
Late pregnacy
sFLT1
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