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SPOTLIGHT REVIEW

Pregnancy as a cardiac stress model

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Cardiac hypertrophy occurs during pregnancy as a consequence of both volume overload and hormonal changes. Both pregnancy- and exercise-induced cardiac hypertrophy are generally thought to be similar and physiological. Despite the fact that there are shared transcriptional responses in both forms of cardiac adaptation, pregnancy results in a distinct signature of gene expression in the heart. In some cases, however, pregnancy can induce adverse cardiac events in previously healthy women without any known cardiovascular disease. Peripartum cardiomyopathy is the leading cause of non-obstetric mortality during pregnancy. To understand how pregnancy can cause heart disease, it is first important to understand cardiac adaptation during normal pregnancy. This review provides an overview of the cardiac consequences of pregnancy, including haemodynamic, functional, structural, and morphological adaptations, as well as molecular phenotypes. In addition, this review describes the signalling pathways responsible for pregnancy-induced cardiac hypertrophy and angiogenesis. We also compare and contrast cardiac adaptation in response to disease, exercise, and pregnancy. The comparisons of these settings of cardiac hypertrophy provide insight into pregnancy-associated cardiac adaptation.

Keywords Pregnancy • Physiological cardiac hypertrophy • Hormones • Signalling pathways • Molecular signatures

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1. Introduction

In general, cardiac hypertrophy is used as a prognostic indicator for heart disease and heart failure, but a well-accepted exception to this paradigm is exercise-induced cardiac hypertrophy, sometimes referred to as athlete's heart.[1] Cardiac hypertrophy is defined as an increase in heart muscle mass with changes in cardiac geometry. Pathological stimuli, such as pressure overload in response to arterial hypertension or aortic stenosis, initially activate an adaptive increase in mass to compensate for the increase in workload. Volume overload caused by mitral or aortic insufficiency results in increase in ventricular dimension. Both pressure and volume overload initially change chamber morphometry. As shown in *Figure 1*, the change in geometry can be either concentric (i.e. relatively greater increase in wall thickness with small cavities) or eccentric (i.e. enlarged ventricular cavities with relatively thin walls), but such hearts often progress to a maladaptive phase which is accompanied by decreased cardiac function and heart failure.[1] Thus, these conditions are called pathological cardiac hypertrophy. In contrast to pathological cardiac hypertrophy, exercise-induced cardiac hypertrophy is called physiological, and in this setting, the function of the heart is either normal or enhanced.[1] Exercise generally results in proportional increases in chamber dimension and wall thickness.[2]

In addition to distinguishable structural and functional phenotypes between physiological and pathological cardiac hypertrophy, numerous criteria distinguish them. These include distinct stimuli, molecular and signalling cascades, metabolic aspect, and capillary density/angiogenesis (*Table 1*). For example, cardiac hypertrophy that is induced by pregnancy[3–6] and exercise conditioning[7] is reversible, activates 'favourable' structural and molecular signatures, normal or increased angiogenesis, and generally 'favourable' hypertrophic signalling pathways. In contrast, pathological hypertrophy is accompanied by activation of genes normally expressed in foetal development, decreased angiogenesis, and activation of canonical unfavourable signalling cascades.[8,9]

A substantial number of studies[3–6,10,11] and review articles[8,12] have described the enlargement of the heart during pregnancy as 'physiological' as opposed to pathological. In this review, an overview of pregnancy-induced cardiac adaptation is presented to help describe the unique nature of cardiac adaptation during pregnancy and parallel comparisons with exercise-induced cardiac hypertrophy are given where possible.

2. Cardiac hypertrophy and reversibility of cardiac hypertrophy during pregnancy

During pregnancy, the heart develops mild eccentric hypertrophy[10] characterized by an increase in chamber dimension or physiological hypertrophy characterized by a proportional increase in chamber dimension and wall thickness.[6] The length-to-width ratio is well preserved

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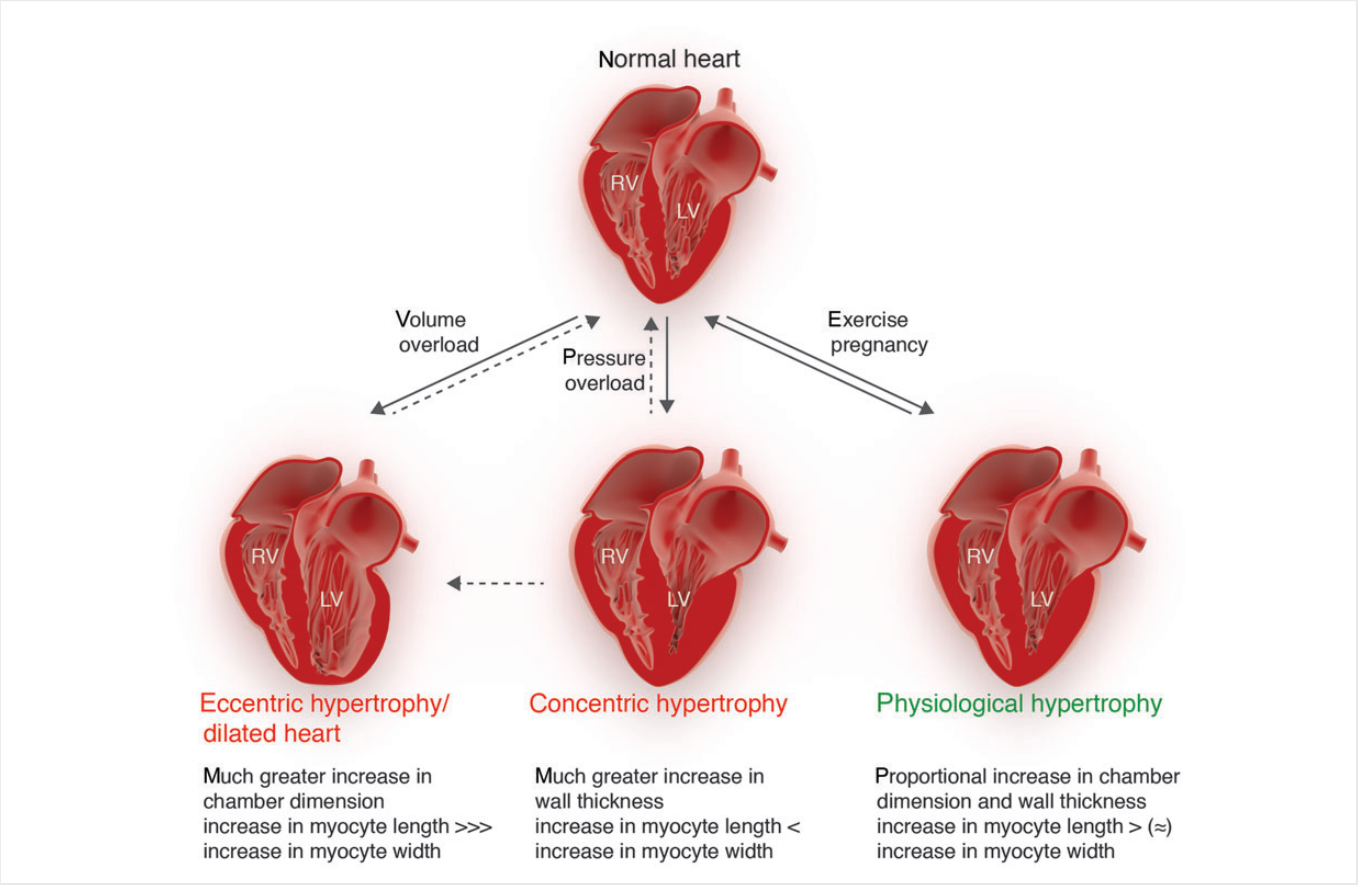

Figure 1 Morphometric alterations in response to various stimuli. See detailed information in Section 3.

Table 1 Key criteria to differentiate physiological from pathological cardiac hypertrophy

	Pregnancy	Exercise	Pathological
Cardiac function	Normal or depressed in late pregnancy	Normal or enhanced	Decreased
Reversibility	Reversible	Reversible	Irreversible
Foetal gene induction	Relatively normal	Relatively normal	Usually up-regulated
Fibrosis	None	None	Increased
Capillary density/angiogenesis	Normal	Normal or increased	Decreased
Signalling pathway	PI3K/Akt, ERK1/2, and calcineurin	PI3K/Akt	Gaq (MAPKs and calcineurin)

in left ventricular myocytes isolated from pregnant rats.[13] Thus, mild eccentric hypertrophy in response to pregnancy[10] and exercise[14] is distinct from the pathological state of dilated and failing hearts which have a much greater increase in chamber dimension with relatively thin walls[2] or a much greater increase in the myocyte length compared with the width[15] (*Figure 1*).

The question has been raised of whether the important determinant for physiological vs. pathological hypertrophy is the duration of each stimulus. However, Perrino *et al.*[16] demonstrate that intermittent pressure overload on the hearts of mice still triggers cardiac dysfunction.[16] In addition, pregnancy is associated with continuous volume overload, but does not lead to long-term cardiac dysfunction, indicating that the nature of the stimulus, not the duration of the stimulus, distinguishes the two types of cardiac hypertrophy.

Pathological hypertrophy in response to pressure or volume overload initially is adaptive, but can lead cardiac dilation and systolic and diastolic dysfunction.[1,2] While there are reports of regression of pathological cardiac hypertrophy,[17] at some point, this is irreversible and results in heart failure.[1,2] In contrast, exercise-induced cardiac hypertrophy is reversible following adequate detraining in both humans and laboratory animals.[7,18] Previous studies demonstrate that exercise-induced cardiac hypertrophy regresses as early as 7–14 days to 4 weeks following cessation of exercise[7] in rodents, but the timing depends on training intensity and duration. Similar to exercise training, pregnancy is

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associated with cardiac hypertrophy that is readily reversible as early as 7–14 days post-partum in rodents[5,19] and can take up to a year in humans,[20,21] but the time course of regression depends largely on the lactation status and the number of pregnancies (i.e. slower with lactation[22] and subsequent pregnancies[21]).

3. Stimuli during pregnancy

Pregnancy is associated with prolonged cardiac volume overload secondary to increased blood volume[23] that results in cardiac hypertrophy. In this regard, pregnancy-induced cardiac hypertrophy is somewhat analogous to that obtained by exercise conditioning. However, unlike exercise training, the volume overload and increased heart rate are continuous rather than intermittent. During pregnancy, cardiac output increases gradually and reaches a peak from the second trimester to term.[21] This increase in cardiac output is paralleled with either gradual and substantial increases in heart rate[24] and stroke volume or a fall in vascular resistance.[21,25] Although heart rate is greater during pregnancy, the levels of plasma catecholamine during pregnancy remain unresolved (i.e. no change,[24] decreased,[26] or increased[27] during gestation), primarily due to the methodological difficulties of sample collection and measurement. However, the systemic response to norepinephrine appears to be attenuated during pregnancy.[28] For example, adrenaline infusion in non-pregnant women results in decreased vascular resistance and increased cardiac output, whereas healthy pregnant women do not show these changes.[28] Relaxin is a polypeptide hormone produced by the corpus luteum during pregnancy.[25] The levels of circulating relaxin gradually rise and reach peak concentrations at the end of pregnancy (~100 ng/mL) in rats.[25] The fact that haemodynamic adaptation seen during pregnancy is mimicked by the administration of relaxin in rats suggests that relaxin is a major contributor to pregnancy-associated decreased vascular resistance and increased cardiac output.[25]

In addition, pregnancy is accompanied by significant changes in the sex steroid hormones[29–31] that have been implicated as important mediators of cardiac hypertrophy and anti-hypertrophy. In mice, birth most often occurs at Day 20 with the presence of a copulatory plug counted as Day 1 of pregnancy. In mice, the levels of circulating progesterone rise as early as Day 2 of pregnancy (14.7–18.4 ng/mL),[29,30] and gradually rise in early pregnancy (until Day 9: 34–54 ng/mL).[29–31] Then the levels of progesterone decrease significantly (8–10 days of gestation: 18–27 ng/mL),[29–31] and rise again and peak at Day 15–16 (82–113 ng/mL).[6,29,31] This is followed by a continuous gradual decrease to a low value that is similar to non-pregnant control values, on the day of parturition (0.8–5.5 ng/mL).[29–31] Progesterone has been shown to increase protein synthesis in cardiac muscle[32] and can cause cardiomyocyte hypertrophy.[6] In addition, exogenous administration of progesterone in normally cycling virgin female mice induces cardiac hypertrophy.[33] The pattern of circulating oestradiol is distinct from progesterone, and unlike progesterone, oestradiol is anti-hypertrophic.[34] Serum oestradiol is undetectable in non-pregnant diestrus cycle mice (<10 pg/mL[6]). Levels are high on Day 1 of pregnancy (38.6 pg/mL), but fall to low levels from Day 5 to 16 days of pregnancy (18.9 pg/mL) and only significantly increase in late pregnancy (17–19 days of pregnancy: 60.8–68 pg/mL).[6,30] A summary of serum progesterone and oestradiol levels from various studies is illustrated in *Figure 2*. Oestradiol administration to virgin female guinea pigs mimics some of the haemodynamics of pregnancy, such as an increase in cardiac output by increases in stroke volume and blood volume.[35] In addition, the decrease in cardiac Kv4.3 transcripts in pregnancy is mimicked by the administration of oestrogen to ovariectomized mice.[10] These results show that alterations in sex hormones during pregnancy contribute to pregnancy-induced cardiac adaptation.

Cytokines and chemokines play important roles in cardiac remodelling and physiology, particularly in pathological settings. Previous studies have demonstrated that pathological cardiac hypertrophy induced by prolonged stimulation of isoprenaline[36,37] and pressure overload[38] is accompanied by up-regulation of chemokines, pro-inflammatory cytokines, and related molecules, such as interleukin (IL)-1β, IL-6, tumour necrosis factor-α (TNF-α), transforming growth factor-β_1 (TGF- β_1), and NF-kB. Increased pro-inflammatory cytokines during pathological settings are highly correlated with an increase in fibrosis.[38] In contrast, the hearts of exercise-trained animals do not have increased pro-inflammatory cytokines, such as IL-6, TNF-α, TGF-β_1, and NF-kB,[36,39] whereas another study[36] shows that anti-inflammatory cytokine, IL-10, is significantly increased. Mice lacking functional IL-6 are not blocked in exercise-induced

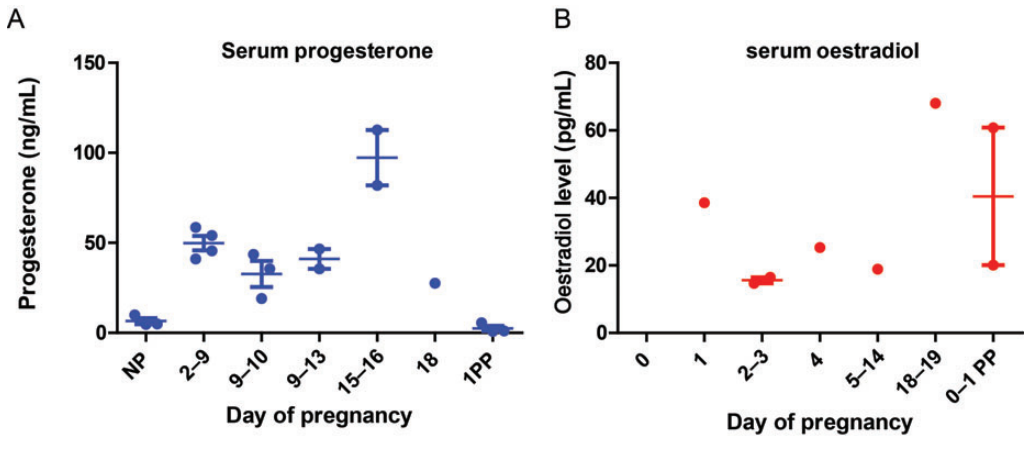

Figure 2 Circulating sex hormones during pregnancy in mice. (*A*) Serum progesterone levels in mice during pregnancy. Progesterone increases in early pregnancy and decreases slightly in mid-pregnancy and reach its peak value in 15–16 days of pregnancy.[6,29–31] (*B*) Serum oestradiol levels in mice during pregnancy. Values from previous studies.[6,30] Day of gestation is grouped together based on previous reports to show the pattern of changes of hormones. Values are means ± SEM.

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cardiac hypertrophy. In addition, exercise training in a model of β-adrenergic hyperactivity attenuates cardiac dysfunction and fibrosis by inhibiting pro-inflammatory cytokines.[36] However, there are contradictory results of adaptation of skeletal muscle to exercise training, demonstrating that IL-6 is significantly increased in working skeletal muscles.[40]

It has been suggested that the maintenance of pregnancy is mediated by a balance between pro- and anti-inflammatory cytokines.[41] Serum IL-6 gradually increases during pregnancy,[42,43] whereas IL-10 levels are higher in late pregnancy and during labour without altering TNF-α.[43] Leukaemia inhibitory factor (LIF) is an important cytokine for the establishment of pregnancy.[44] LIF has been shown to attenuate fibrosis by reducing collagen production, but it also can induce contractile dysfunction and induction of foetal gene programme.[45] The role of cytokines in the cardiac hypertrophy that occurs during pregnancy has not been studied.

4. Cardiac function during pregnancy

One of the most important features that distinguishes physiological cardiac hypertrophy from pathological cardiac hypertrophy is function; normal or enhanced function in the former but decreased function in the latter.[12] Left ventricular function is determined by several parameters, such as loading conditions (pre-load and afterload), myocardial contractile properties, and heart rate. There is consensus that exercise-induced cardiac hypertrophy is associated with normal or enhanced cardiac function in all of these parameters.[46] However, there are inconsistent reports of left ventricular function during pregnancy. For example, cardiac output increases gradually and reaches a peak from the mid-trimester to term.[21,47] The increase in cardiac output in early pregnancy is largely due to gradual and substantial increases in stroke volume. The further increase in cardiac output mid- to late pregnancy is primarily due to an increase in heart rate[23,47] and a fall in afterload via decreased total vascular resistance.[21,47] Increased stroke volume is primarily due to an increase in pre-load by a pregnancy-associated increase in blood volume.[23,31,32] However, reports of systolic function indicated by ejection fraction or fractional shortening typically obtained from echocardiography assessment during pregnancy are somewhat inconsistent. Some studies have described function as normal,[47] but others have described decreased function.[3,6,10,48,49] Mild impairment of left ventricular diastolic function[49] has also been reported in later stages of human pregnancy. These discrepancies seem likely to be due to the different gestational ages when measurements were made (early phase of third trimester[47] vs. later phase of third trimester[48]). Consistent with function being different in different stages of pregnancy, animal studies show that during late pregnancy (i.e. 1–2 days before delivery), systolic function indicated by ejection fraction or fractional shortening is significantly decreased.[6,10] The fact that function appears to be transiently reduced in late pregnancy does distinguish it from exercise-induced cardiac adaptation. However, it is noteworthy that ejection fraction or fractional shortening is of limited value since these parameters highly depend on pre- and afterload. For example, haemodynamic parameters, measured by Langendorff-perfused isolated mouse hearts, are similar between hearts from non-pregnant controls and late pregnancy.[50] Studies using an isolated working heart preparation, in which pre-load and afterload can be tightly controlled, demonstrate increased velocity of circumferential fibre shortening in pregnant rats compared with non-pregnant controls.[51] This suggests an adaptation in myocardial contractile function during pregnancy.[51] Thus, it is important to note that many review papers[1,8,12] and original articles[4,6,10,48] describe pregnancy-induced cardiac hypertrophy as purely physiological. That said, the cardiac contractile dysfunction, especially load-dependent echocardiography assessment in late pregnancy is transient rather than persistent, and is reversible during the post-partum period with no significant long-term detrimental effects on cardiac function.[11]

5. The structural phenotype of the heart and its regulation during pregnancy

Another significant difference between pathological and physiological cardiac hypertrophy is their distinct histological features. In the healthy heart, extracellular matrix provides a supporting framework, and a rigorously controlled balance between the synthesis and breakdown of its component proteins.[52] In response to pathological stimuli, cardiac collagen deposition disproportionally occurs and leads to an increase in interstitial fibrosis.[53] Increased interstitial fibrosis contributes to mechanical stiffness of the heart and leads to diastolic dysfunction and progresses to systolic dysfunction.[54] Both matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) regulate the extracellular matrix. MMPs reside in the interstitial space and degrade collagen and other proteins, whereas TIMPs oppose the activity of MMPs. One of the mechanisms for heart failure due to adverse ventricular remodelling is the dysregulation of MMPs and TIMPs.[55] In a decompensated heart failure model, MMP3, TIMP1, and TIMP2 levels are up-regulated with a significant increase in collagen I deposition,[56] an increase in the collagen I/III ratio,[57] and a decrease in the elastin/collagen I ratio.[58] In chronic pressure overloaded human hearts,[59] these are increases in the expression of TIMP1 and TIMP2, the TIMP1/MMP2 ratio, and TIMP2/MMP2 ratio. In the myocardial infarction model, mRNA expression of collagen I and III are significantly increased.[60] These increases are highly correlated with the degree of interstitial fibrosis.[59]

In contrast, neither pregnancy- nor exercise-induced cardiac hypertrophy is associated with fibrosis.[6,11,61] We previously demonstrated that extracellular matrix-related genes are the most significantly up-regulated group of genes in late pregnancy and immediate post-partum,[11] but histological analysis shows that fibrosis does not occur in the hearts of pregnant[6,61] and post-partum mice.[19] We show that MMP3 is significantly up-regulated in late pregnancy and immediate post-partum, while TIMP1 is significantly up-regulated in immediate post-partum.[19] Thus, the MMP3/TIMP1 ratio is well maintained during pregnancy, unlike pathological hypertrophy showing at a significant increase in the TIMP1/MMP2 ratio.[59] This is also true in exercise-induced cardiac hypertrophy.[11] A recent study demonstrates that the pregnancy hormone, relaxin, has anti-fibrotic properties by modulating MMP activity and collagen synthesis.[62] Together, these results suggest that genes related to the cleavage and inhibition of cleavage of extracellular matrix proteins are involved in physiological cardiac adaptation, but fine tuning of MMPs and TIMPs differentiate physiological into pathological cardiac hypertrophy.

6. Foetal gene induction during pregnancy

It has been generally accepted that pathological hypertrophy induced by pressure overload is associated with up-regulation of foetal genes, including arterial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), and genes for foetal isoforms of contractile proteins, such as

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Table 2 Foetal gene induction during pregnancy-, exercise-, and pressure-overload induced cardiac hypertrophy

	Pregnancy		Exercise	Pressure-overload[9]
	MP	LP		
α-MyHC	=[6]	=[6,10]	↑[60]=[46]	↓
β-MyHC	=[6]	=[6,10]↑[63]	↓[66]=[46,60]	↑
α-Skeletal actin	=[6]	=[6]	=[60]	↑
SERCA2A	=[6]	=[6,10]		↓
ANF	↓[6]	=[6,10]	↑[9,63,64] =[60]↓[65]	↑
BNP	=[6]	=[6]↓[63]		↑

MyHC, myosin heavy chain; SERCA2A, cardiac Ca^{2+}-ATPase of the sarcoplasmic reticulum ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; LP, late pregnancy; MP, mid-pregnancy; =, no change; ↓, decrease; ↑, increase.

α-skeletal actin and β-myosin heavy chain (MyHC) with down-regulation of genes normally expressed at high levels in the adult murine hearts, such as α-MyHC and sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2A).[8,9,63] However, foetal gene induction during physiological hypertrophy does not follow a unique pattern of expression (see *Table 2*). For example, ANP expression is up-regulated in some exercise-induced cardiac adaptation,[9,63,64] whereas others show down-regulation[65] or no change in ANP expression.[60] One study shows a significant increase in α-MyHC expression without altering β-MyHC,[60] whereas others show a significant decrease in β-MyHC[66] in exercise-induced cardiac hypertrophy. ANP levels are significantly decreased in mid-pregnancy, but BNP, SERCA2, phospholamban, α-skeletal actin, α-MyHC, and β-MyHC do not change in mid- and late pregnancy.[6,10] On the other hand, in a different study, β-MyHC expression is reported to be increased and BNP is decreased in late pregnancy.[63] It has been shown that increased levels of α-skeletal actin are correlated with increased[67] or decreased[68] myocardial contractile function. Moreover, the experimental intermittent pressure overload that is associated with cardiac dysfunction does not induce the foetal gene programme.[16] Thus, the biological consequences of foetal gene programme activation remain unresolved.

7. Metabolism of the heart during pregnancy

While the normal healthy adult heart utilizes lipids as its main fuel source, the pathological heat shows a shift from fatty acid oxidation to glucose metabolism.[69] Consistent with the induction of foetal gene expression in response to pathological stimuli, this metabolic profile recapitulates the 'foetal' metabolic profile that prefers carbohydrate metabolism, mainly through anaerobic glycolysis.[69] In heart failure, oxidative capacity and mitochondrial enzyme activities are decreased.[70] In contrast, a physiological cardiac stimulus such as endurance exercise training increases cardiac oxidative capacity, mitochondrial enzyme activity, and lipid metabolism.[63] Limited studies are available regarding the metabolism of the heart during pregnancy. Although an increased contribution of carbohydrate metabolism measured by respiration calorimetry was reported in late pregnancy,[71] genes regulating carbohydrate pathways (i.e. PDK4 and GLUT4) are not altered.[63] Peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α, the master regulator of mitochondrial biogenesis, was increased in mid-pregnancy,[33] whereas no alteration in oxidative capacity and decreased genes regulating fatty acid oxidation were seen in late pregnancy.[63] Further research is needed to elucidate the metabolic pathways during pregnancy since metabolic perturbations, such as gestational diabetes mellitus, are common during pregnancy.[72]

8. Signalling pathways that differentiate physiological from pathological cardiac hypertrophy

Accumulated evidence in transgenic and knockout animal models has shown that signalling pathways induced by exercise conditioning can be distinct from those induced in pathological models.[73,74] Thus far, phosphatidylinositol-3-kinase (PI3 K)/Akt signalling pathways have been implicated in exercise and the Gαq pathways have been associated with pathological cardiac adaptation.[75] However, it is noteworthy that there is cross-talk between the two pathways.[6] *Figure 3* illustrates simplified the schematic view of signalling pathways in the heart.

8.1 The PI3 K/Akt pathway is an important mediator of pregnancy- and exercise-induced cardiac hypertrophy

A large number of studies suggest that exercise-induced cardiac hypertrophy is mediated by signalling through the PI3 K pathway.[75] For example, the expression of constitutively active PI3K-α (p110α or caPI3K) in the heart results in significant cardiac hypertrophy with normal contractility, and does not transit into a maladaptive hypertrophy.[76] Conversely, cardiac expression of a mutant dominant-negative p110α (dnp110α) and inactivation of the regulatory subunit of PI3K in mice displays blunted exercise-induced hypertrophy with normal cardiac function in response to swim training but not pressure overload.[74]

The major downstream cascade of the PI3K signalling is protein kinase B (Akt) and glycogen synthase kinase 3β (GSK3β). Studies from wild-type (WT) mice[74,77] and transgenic mouse models suggest that Akt signalling is important in exercise-induced cardiac hypertrophy[73] as well as in cardiac protection against pathological insults.[78] Mice with cardiac-specific constitutive activation of Akt (caAkt) or myristoylation (myr-Akt) have increased myocardial mass with normal systolic function.[78] These mice have a remarkable increase in cardiac contractility,[79] and are protected from apoptosis[80] and ischaemia-reperfusion (IR) injury.[78] In contrast, mice with targeted disruption of the Akt1 gene do not undergo exercise-induced cardiac hypertrophy but demonstrate exacerbated pressure overload-induced cardiac hypertrophy compared

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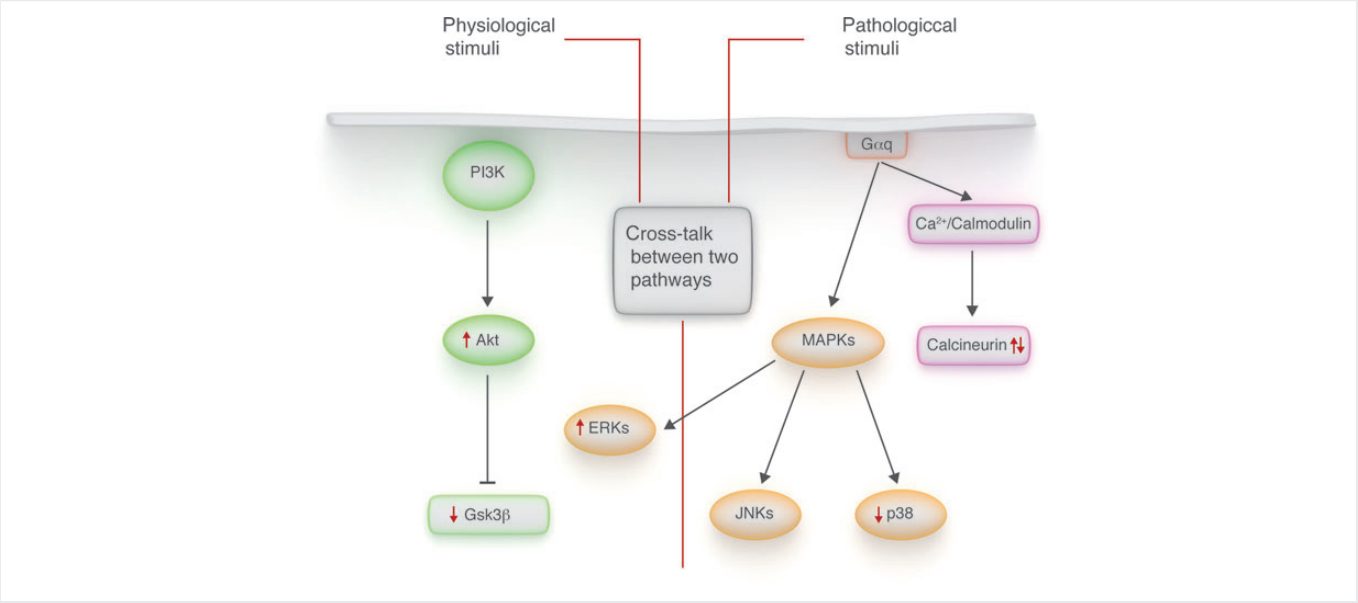

Figure 3 A simplified schematic view of signalling pathways in the heart. Red arrows represent signalling molecules that are altered during pregnancy. See detailed information in Section 8.

with WT mice.[73] However, it appears that long-term Akt activation may also result in pathological hypertrophy.[78] Mice expressing a cardiac-specific active (anti-hypertrophic) form of GSK3β (caGSK3β), a downstream target of Akt, have smaller hearts than WT mice in basal condition and are blocked in pathological hypertrophy.[81]

We[6] and others[4] demonstrate that pregnancy-induced cardiac hypertrophy is also mediated by Akt and its downstream molecules. The activity of Akt, as assessed by the ratio of phospho-Akt to total Akt, is significantly increased during pregnancy.[4,6,82] The downstream targets of Akt, including GSK3β, ribosomal S6 protein kinase (p70S6 K), and mammalian target of rapamycin (mTOR), are increased only in mid-pregnancy, but not in late pregnancy.[6] Consistent with the idea that activation of Akt/GSK3β is an important mediator of pregnancy-induced cardiac hypertrophy; hypertrophic responses of hearts from myr-Akt or caGSK3β mice are attenuated.[6] Taken together, these studies suggest that pregnancy-induced cardiac hypertrophy is mediated by Akt and its downstream targets.[4,6,82]

8.2 Gαq and MAPK signalling pathways in pregnancy

Gαq and the downstream consequences of Gαq activation have been implicated as important mediators of pathological cardiac hypertrophy. Targeted overexpression of a constitutively active Gαq in mice induces pathological cardiac hypertrophy with excessive apoptosis,[83] whereas cardiac-specific transgenic mice that inhibits Gαq-mediated signalling do not develop pressure overload-induced cardiac hypertrophy.[84] The downstream targets of Gαq are mitogen-activated protein kinases [MAPKs; extracellular signal-regulated kinase (ERK1/2), p38, and c-Jun amino-terminal kinase] and the calcium-dependent signalling molecule calcineurin. Previous studies show that ERK1/2[77] and other MAPKs[85] are not regulated in exercise-induced cardiac hypertrophy, whereas pressure overload-induced cardiac hypertrophy is accompanied by an increase in p38 phosphorylation.[34] However, transgenic mouse models of MAPK manipulation raise several questions regarding the importance of MAPKs in pathological cardiac hypertrophy. Mice expressing cardiac-specific constitutively active MAPK kinase 1 (MEK1), which is immediately upstream of ERK1/2, but does not activate JNK or p38, have cardiac hypertrophy with improved cardiac function (a hallmark of physiological hypertrophy).[86] Mice lacking apoptosis signal-regulating kinase 1, which is upstream of p38, have less cardiac hypertrophy and less apoptosis in response to pressure overload,[87] but much greater exercise-induced cardiac hypertrophy compared with WT mice.[88] Unlike exercise-induced cardiac hypertrophy, phosphorylation of ERK1/2 is significantly increased in mid-pregnancy, whereas phosphorylation of p38 is significantly decreased during pregnancy.[3,64] Because progesterone but not oestradiol levels are significantly increased in mid-pregnancy, we have investigated a causal relationship between progesterone and ERK1/2.[6] Progesterone treatment induces myocyte hypertrophy and phosphorylation of ERK1/2. When ERK1/2 is blocked by PD98059, a specific inhibitor of MEK1, progesterone-induced cellular hypertrophy is blocked.

Another downstream pathway of the Gq signalling is the calcium-dependent protein phosphatase, calcineurin. Calcineurin has been strongly implicated as an important player in pathological hypertrophy and heart disease.[89] Calcium activates calcineurin which dephosphorylates cytoplasmic nuclear factor of activated T cells (NFAT), inducing translocation of NFAT to the nucleus. NFAT then activates pro-hypertrophic genes.[1] Numerous studies have shown that calcineurin activity is increased in the hearts of patients with cardiac hypertrophy and heart failure,[90] and inhibition of this pathway with cyclosporine A (CsA) can delay the progression to pathological heart failure in animal models.[91] However, other reports demonstrate that inhibition of calcineurin exacerbates pathological cardiac disease.[92] The role of calcineurin in exercise-induced cardiac hypertrophy remains controversial.[89,93,94] For example, calcineurin protein levels are reduced after voluntary wheel running training in mice,[94] whereas cardiac NFAT reporter mice do not change calcineurin activity following swim training.[89] One study shows that treatment with CsA does not block exercise-induced cardiac hypertrophy,[9] whereas

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another study demonstrates that treatment with CsA completely blocks exercise-induced cardiac hypertrophy.[93] Our recent study shows that calcineurin levels and activity are increased in early pregnancy.[33] More important through the administration of the CsA treatment, we show that calcineurin activity is required for pregnancy-induced cardiac hypertrophy.[33] Calcineurin inhibition also blocks ERK1/2 and Akt activation. However, unlike pathological cardiac hypertrophy, the regulation of calcineurin is biphasic showing a significant increase in early pregnancy, but a significantly decrease in late pregnancy.[33,63] Taken together, pregnancy-induced cardiac hypertrophy is modified by calcineurin, ERK1/2, Akt and its downstream targets, and these signalling cascades are regulated in a temporal manner. In addition, calcineurin activation in early pregnancy transiently initiates the pathways responsible for the development of physiological hypertrophy (*Figure 4*).

9. Angiogenesis in pregnancy

The relative balance between the growth of cardiac muscle mass and coronary angiogenesis is a critical determinant of physiological vs. pathological cardiac hypertrophy.[95] Exercise-induced cardiac

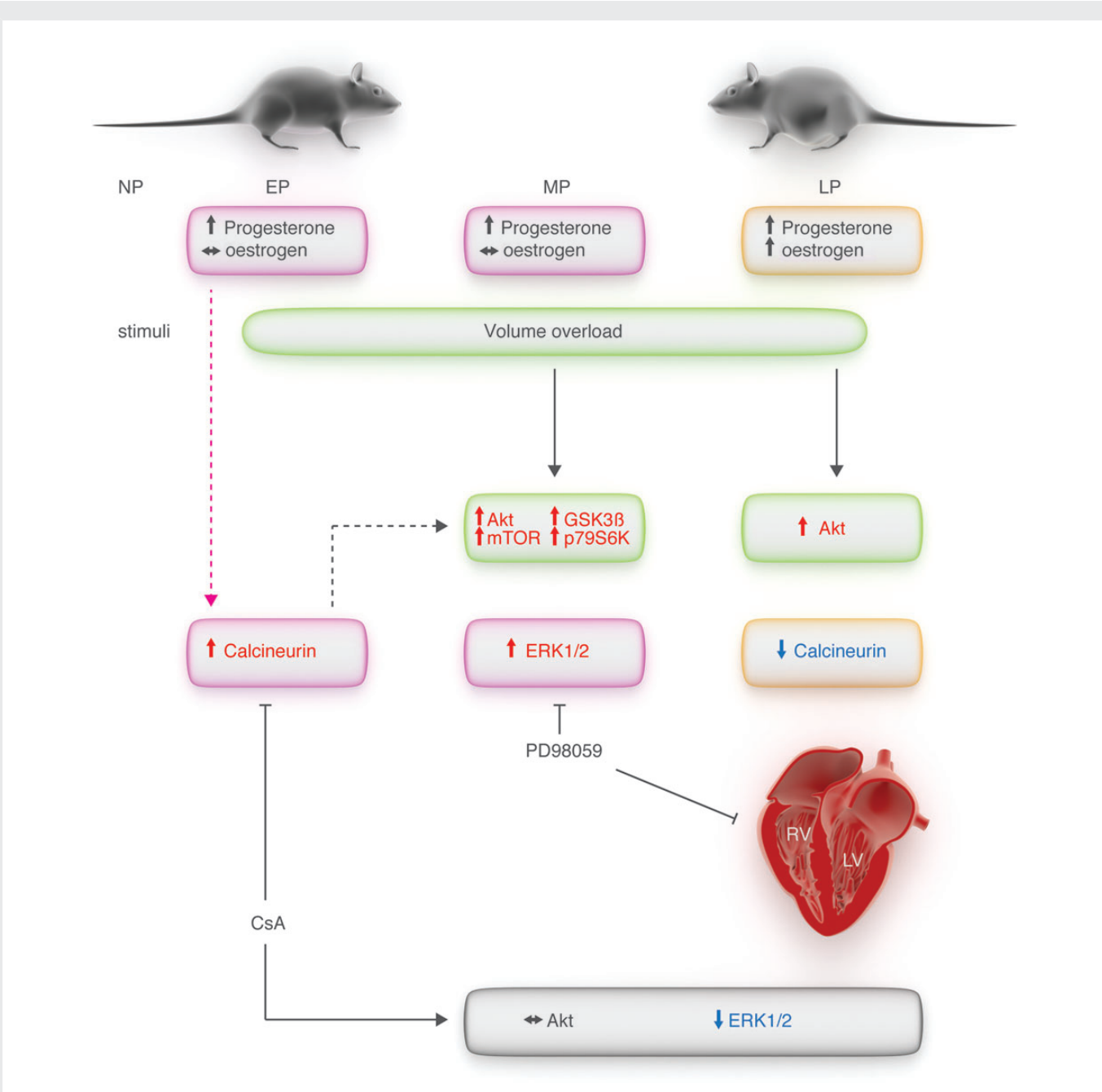

Figure 4 Signalling pathways in pregnancy-induced cardiac hypertrophy. Pregnancy is associated with prolonged cardiac volume overload and changes in hormonal milieu, which results in cardiac hypertrophy. Increased progesterone level in early pregnancy activates calcineurin. This increase in calcineurin activity transiently initiates pathways, such as Akt and its downstream targets, and ERK1/2 that are responsible for the development of physiological hypertrophy. Calcineurin inhibition by CsA treatment in early pregnancy blocks Akt and ERK1/2 activation, and blocks pregnancy-induced cardiac hypertrophy. A specific inhibitor of MEK 1 (PD98059), which is immediately upstream of ERK1/2, blocks progesterone-mediated isolated neonatal myocyte hypertrophy.

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hypertrophy is accompanied by a proportional increase in cardiac capillary density,[96] whereas pathological hypertrophy induced by pressure overload is correlated with a reduction in capillary density.[53] During pregnancy, myocardial angiogenesis, assessed by an increase in both capillary density per cardiomyocyte and vascular endothelial growth factor A (Vegfa), is significantly increased.[19,82] In addition, mRNA levels of angiogenic factors, such as PGC-1α (Pgc1a), Vegfa, angiogpietin-1, and fibroblast growth fact 2, are significantly increased in early to mid-pregnancy, but return to non-pregnant control levels in late-pregnancy.[33] It has been suggested that the placenta secretes VEGF inhibitors such as soluble fms-like tyrosine kinase 1, which create an antiangiogenic environment in late pregnancy, and this is more pronounced in pre-eclampsia and in multiple pregnancies.[97] The Akt-mTOR pathway has been suggested to mediate both cardiac growth and angiogenesis.[95] However, prolonged Akt signalling prevents angiogenesis by down-regulation of mTOR-mediated angiogenesis.[98] We have previously shown that phosphorylation of downstream targets of Akt is increased in mid-pregnancy, but they return to non-pregnant control levels in late pregnancy, whereas Akt is activated in mid- to late pregnancy.[6] The prolonged activation of Akt (from mid- to late pregnancy) in the face of elevated mTOR only in mid-pregnancy may lead angiogenic factors to return to non-pregnant control levels. The causal relationship between Akt activation and angiogenesis during pregnancy needs to be further investigated.

10. Summary

Although both exercise- and pregnancy-induced cardiac hypertrophy are considered as physiological, pregnancy-induced cardiac hypertrophy is unique and differs from that induced by exercise training.[11] The data from animals and humans suggest that pregnancy-induced cardiac hypertrophy shares similar characteristics with exercise, including reversibility, structural and molecular phenotypes, and some common signalling pathways, but also have distinct features (*Table 1*). Alterations in female sex hormone levels play a critical role in pregnancy-induced cardiac adaptation.[6,32,33] In particular, progesterone surges in early pregnancy appear to initiate a hypertrophic signalling cascade. Oestradiol surges in late pregnancy (15–16 days of gestation in mice)[30] appear to initiate cardiac remodelling in postpartum,[33] but more studies need to be done on the role of oestradiol in regression of cardiac hypertrophy following pregnancy. As shown in *Figure 4*, pregnancy-induced cardiac hypertrophy is very dynamic and signalling cascades are altered over the time course of pregnancy. The stimuli of both exercise and pregnancy can result in cardiac pathology. For example, sudden death can occur in athletes,[99] and pregnancy can be associated with adverse events such as the often fatal peripartum cardiomyopathy[97,100] and more vulnerable to the IR injury in late-pregnancy.[50] Although hearts from late pregnancy appear to operate in the edge of dysfunction,[6,10,50] the decreased cardiac function following IR injury is fully restored to the levels of the non-pregnant controls after 7 days post-partum.[50] Thus, we can conclude that pregnancy-induced cardiac hypertrophy displays many of the hallmarks of physiological hypertrophy.

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