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Review Article

New frontiers in heart hypertrophy during pregnancy

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Abstract: During Pregnancy, heart develops physiological left ventricular hypertrophy as a result of the natural volume overload. Previously we have characterized the molecular and functional signature of heart hypertrophy during pregnancy. Cardiac hypertrophy during pregnancy is a complex process that involves many changes including in the signalling pathways, composition of extracellular matrix as well as the levels of sex hormones. This review summarises the recent advances and the new frontiers in the context of heart hypertrophy during pregnancy. In particular we focus on structural and extracellular matrix remodelling as well as signalling pathways in pregnancy-induced physiological heart hypertrophy. Emerging evidence shows that various microRNAs modulate key components of hypertrophy, therefore the role of microRNAs in the regulation of gene expression in pregnancy induced hypertrophy is also discussed. We also review the role of ubiquitin proteasome system, the major machinery for the degradation of damaged and misfolded proteins, in heart hypertrophy. The role of sex hormones in particular estrogen in cardiac remodeling during pregnancy is also discussed. We also review pregnancy-induced cardiovascular complications such as peripartum cardiomyopathy and pre-eclampsia and how the knowledge from the animal studies may help us to develop new therapeutic strategies for better treatment of cardiovascular diseases during pregnancy. Special emphasis has to be given to the guidelines on disease management in pregnancy.

Keywords: Pregnancy, physiological heart hypertrophy, signalling pathway, peripartum cardiomyopathy, preeclampsia

Pregnancy-induced physiological heart hypertrophy

Cardiac hypertrophy, defined as an enlargement of the ventricles, is an important compensatory response so the heart can maintain its pumping capacity. Cardiac hypertrophy is often triggered when the heart is subjected to hemodynamic stress from volume or pressure overload [1]. Sustained pressure overload often leads to concentric hypertrophy, which is characterized by increased wall thickness without a concomitant chamber enlargement. Volume overload, on the other hand leads to eccentric hypertrophy characterized by a proportional enlargement of the chamber size and the wall thickness [2]. Heart hypertrophy can be physiological which is beneficial and adaptive or pathological which is maladaptive and detrimental (**Figure 1**). Pathological heart hypertrophy often leads to heart failure if the stimulus persists for a long time. Heart failure is a clinical syndrome attributable to many factors, which begins as a compensatory response to hypertrophic stimuli, followed by a decompensatory response which eventually results in failure. Physiological hypertrophy which occurs, in response to normal exercise or pregnancy, is not associated with fibrosis, dysfunction, or increased morbidity and mortality. Physiological hypertrophy enables the heart to fulfill its function, and is often reversible without significant long-term detrimental effects on cardiac function [3-5]. In these aspects, pregnancy- and exercise-induced hypertrophies are similar. However, pregnancy is also accompanied by drastic hormonal changes. Both estrogen and testosterone steadily increase and reach their maximum levels at the end of pregnancy. In addition during pregnancy, unlike exercise, the force demand placed on the heart is continuous as opposed to sporadic. Still little is known about the molecular mechanisms that mediate

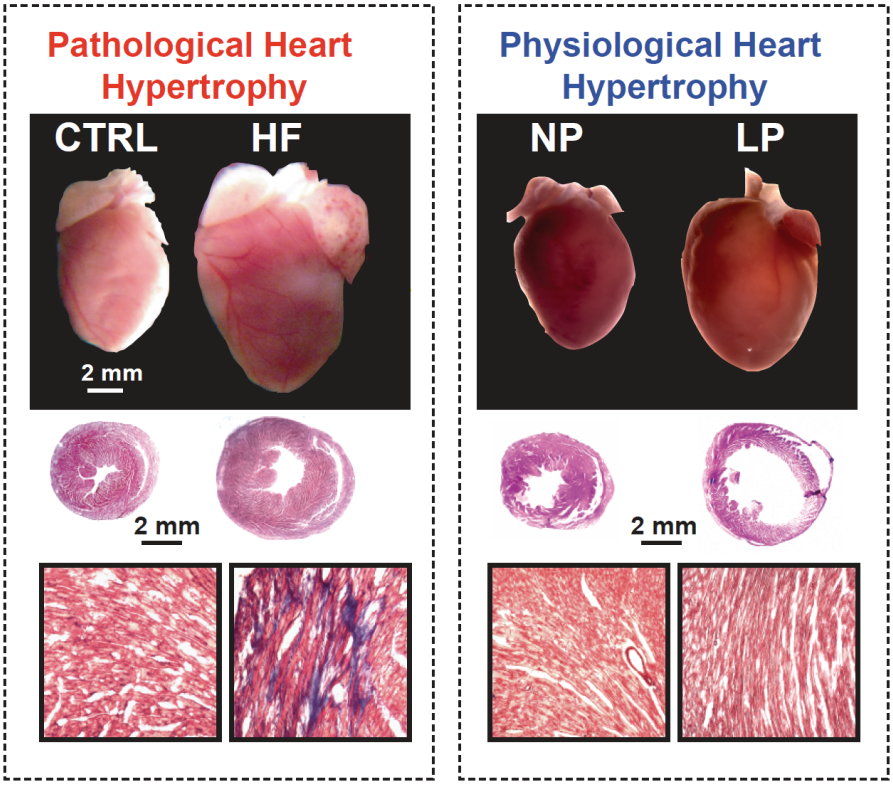

Figure 1. Pathological hypertrophy *vs* pregnancy induced physiological hypertrophy. Top panels: Images of the whole heart in pathological hypertrophy and physiological hypertrophy in late pregnancy in mice; Middle panels: Hematoxylin-eosin staining of heart cross-sections; Bottom panels: Masson trichrome staining of heart cross sections, blue colour indicates fibrosis. CTRL: control; HF: heart failure; NP: non-pregnant; LP: late pregnant.

pregnancy-induced hypertrophy, but recent reports have shown that its molecular signature is unique and differs from that induced by exercise[6].

Changes in cardiovascular system during pregnancy

During pregnancy, there is a global increase in the metabolic demand, and changes in the cardiovascular system must occur to meet these needs. Increased blood volume, increased heart rate, together with reduced systemic vascular resistance all lead to increased cardiac output (**Table 1**). Although pregnancy is associated with hypervolemia partly due to increased retention of water and sodium, the blood pressure is decreased, the renin-angiotensin system is activated and the circulating levels of Angiotensin-II are also increased as the pregnancy progresses [7-9]. The healthy women without heart disease adapt well to these drastic changes that occur during pregnancy. These changes in hemodynamic parameters slowly return to normal values in postpartum period, but complete resolution may take as long as 6 months after delivery.

Structural and extracellular matrix remodeling of the heart during pregnancy

The extracellular matrix (ECM) is an integral part of several tissues and organ systems in the body. In the heart, fibroblasts are the predominant cell type and are primarily responsible for secreting the proteins that compose the cardiac ECM [10]. The cardiac ECM is a network of proteins that provides structural support and facilitates mechanical, electrical and chemical signals during homeostasis and in response to physiological stress or injury. The cardiac ECM maintains a dynamic homeostasis.

Integrins, collagens, fibronectins and other ECM proteins serve to anchor cells to one another and to the ECM. Matrix metalloproteinases (MMPs) and the related A Disintegrin And Metalloproteinase (ADAM) families function to degrade these ECM anchoring proteins. ADAMs and MMPs are in turn inhibited by tissue inhibitors of metalloproteinases (TIMPs). All these players function in equilibrium to maintain the cardiac ECM [10].

However, disruptions in this homeostasis, called

Table 1. Hemodynamic and hormonal changes in pregnancy, peripartum and post partum

	Pregnancy	Peripartum	Postpartum
Human			
Blood volume	↑[123]	↑[123]	↓[123]
Systolic blood pressure	↓[123]	↑[123]	↑[123]
Diastolic blood pressure	↓[123]	↑[123]	↑[123]
Systemic vascular resistance	↓[123]	↑[123]	↑[123]
Heart rate	↑[123]	↑[123]	↓[123]
Stroke volume	↑[123]	↑[123]	↑[123]
Cardiac output	↑[123]	↑[123]	↑[123]
Estradiol			
Human	↑ gradually[124]	↑ before birth, ↓after birth[124]	↓[124]
Rat	↑ gradually[125]	↑ before birth, ↓after birth[125]	↓[125]
Baboon	↑ gradually[126]	stays high[126]	↓[126]
Progesterone			
Human	↑ gradually[124]	↑ before birth, ↓after birth[124]	↓[124]
Rat	↑ gradually[125]	↓[125]	↓[125]
Baboon	↑ gradually[126]	stays high[126]	↓[126]
Testosterone			
Human	↑gradually (↑↑male fetus, ↑female fetus) [127]	unknown	↓[128]
Rat	↑ gradually[125]	↑ up to day 20, ↓ right before birth, ↓ after birth[129]	↓[129]
Baboon	↑ gradually[126]	stays high[126]	↓[126]
Prolactin			
Human	↑[130]	↑ before birth, stays high after birth if lactating ↑[131,132]	Stays high during lactation[131,132]
Angiotensin			
Human	↑[9,133,134]	↑before birth, ↓sharply 2hr after birth and ↑ afterwards [135]	Unknown

Changes reflect the hemodynamic and hormonal status of women unless otherwise specified. In women, pregnancy refers to week 1 to 36 of gestation, peripartum refers to the last four weeks pre-partum and the first week post-partum and post-partum reflects the first 3-6 months after delivery. For rat, pregnancy reflects the first 20 days of pregnancy, peripartum refers to the last 4 days of gestation and one day after delivery, and post-partum is one week after parturition. For baboons, pregnancy refers to the first 24 weeks of pregnancy, peripartum refers to one week before delivery up to one week post-delivery and post-partum is 11 weeks after birth.

ECM remodeling, are emerging as key processes during cardiac hypertrophy, heart failure and recovery, including dilated cardiomyopathy, myocardial infarction, and hypertensive cardiac hypertrophy [11].

Collagen

Collagen is among the most abundant proteins of the cardiac ECM and is a key structural protein responsible for anchoring cells to each other and to the ECM. Excess collagen deposition in the extracellular space, called fibrosis, is a well documented change that occurs during pathological ventricular remodeling [12]. Fibrosis normally accompanies the inflammatory response during cardiac stress and inhibits contractile function and electrical signal conduction in the heart [13]. Fibrosis also occurs in exercise-induced cardiac hypertrophy [14]. Interestingly, there have been some reports that fibrosis is minimal or absent in the overloaded pregnant heart [15,16].

Integrins

Integrins are membrane-spanning structural proteins that mediate interactions between the

ECM, cardiomyocytes, and cardiac fibroblasts. Integrins have receptor function, mediate cell-cell communication in the heart, and can have diverse downstream responses [12]. This class of proteins has been found to play a vital role in cardio-protective signaling in the failing myocardium, and also in the prevention of fibrosis leading to heart failure [17,18]. Integrins also inhibit cardiomyocyte apoptosis during failure and contribute to the mechanochemical signaling which leads to hypertrophy [19]. Integrins have been reported to be downregulated in models of heart failure [17, 18, 20]. Their role in pregnancy has not been characterized.

Matrix Metalloproteinases (MMPs), Disintegrin Metalloproteinases (ADAMs), and Tissue Inhibitors of Metalloproteinases (TIMPs)

Matrix Metalloproteinases are a family of extracellular matrix degrading enzymes that have been implicated in causing adverse remodeling which results in ventricular dysfunction [10, 12, 21, 22]. ADAMs are a closely related family of matrix degrading enzymes that in addition to their metalloproteinase function also have a disintegrin domain. The study of ADAMs in heart failure is a recently emerging field, and ADAMs are proving to be promoters of adverse ventricular remodeling [12, 23-25].

MMPs and ADAMs are regulated in normal physiological states by a class of molecules called TIMPs. These endogenous molecules tightly regulate MMPs and ADAMs during physiological states. During pathologic ventricular remodeling, the ratio of metalloproteinases to TIMPs is increased and MMPs and ADAMs are not sufficiently regulated [11, 10].

Interestingly, metalloproteinases are also regulated by estrogen [26]. The role of ADAMs and metalloproteinases in the pregnant heart has not yet been explored.

Signaling pathways in pregnancy-induced cardiac hypertrophy

Cardiac hypertrophy is regulated by several receptors and membrane proteins which activate signalling cascades of kinases, phosphatases, and other signalling pathways [27, 28]. The signalling pathways involved in cardiac hypertrophy during pregnancy are complex and differ from pathological hypertrophy pathways [29, 30]. Gonzalez *et al.* characterized several of the signalling pathways involved in pregnancy induced cardiac hypertrophy; however, much remains to be elucidated [31].

Key signalling proteins involved in the development of physiological heart hypertrophy are summarized in **Table 2** and are discussed below.

Akt and GSK3β

Akt signalling plays an important role in mediating survival pathway in cardiac hypertrophy. There are three isoforms of Akt (Akt1, Akt2 and Akt3), Although all three isoforms are broadly expressed, only Akt1 and Akt2 are highly expressed in the heart [32]. Recent studies in Akt knockout mice suggest Akt1 is required for physiological rather than pathological heart growth. Akt1 knockout mice showed a blunted hypertrophic response to swim training but displayed more hypertrophy and cardiac dysfunction in response to pressure overload [33]. It is now generally accepted that Akt1 mediates cardiac cell growth whereas Akt2 is important for cardiac metabolism [33,34]. Akt signalling is known to be upregulated in pathological heart failure as well as exercise-induced cardiac hypertrophy [33-36]. By contrast, Gonazalez *et al.* observe decreased phospho-Akt/Akt expression during pregnancy [31]. Akt signalling activates GSK3β downstream, which mediates anti-hypertrophic signalling in the heart [37-39]. It has been demonstrated that GSK3β negatively regulates heart growth and that inhibition of GSK3β by hypertrophic stimuli was an important mechanism for stimulating growth [40, 41].The role of GSK signalling in the pregnant heart has not been characterized.

ERK 1/2

ERK1/2 mediate anti-hypertrophic signalling in the heart in response to stress. Activated phospho-ERK1/2 is increased in pathological heart hypertrophy induced by trans-aortic constriction [42]. Gonzalez *et al.* show that there is no change in ERK1/2 expression in the heart during pregnancy, indicating that despite its role in pathological heart hypertrophy ERK1/2 does not play a major role in pregnancy-induced cardiac hypertrophy. However, Gonzalez *et al.* also note a brief decrease in ERK1/2 expression immediately following pregnancy and returned

Table 2. Cardiac hypertrophy: physiological vs. pathological hypertrophy

	Physiological Hypertrophy		Pathological Hypertrophy	
	Pregnancy	Exercise	Volume Overload	Pressure Overload
ECM				
Collagen	No change[15,16]	↑[14]	↑[136]	↑[137,138]
MMPs	Unknown	↑[14]	↑activity[139-141]	No change[142]
TIMPs	Unknown	Unchanged[14]	Unchanged[139-141]	No change[142]
ADAMs	Unknown	Unknown	Unknown	Unknown
Integrins	Unknown	Unknown	↓[141]	↓[17,18,20]
Signaling				
STAT3	↑[48]	Unknown	No change[143]	↑[143]
ERK1/2	No change[31]	No change[144]	↑ activity[143], No change in activity [145]	↑ activity[145-148], No change in activity[143]
JNK	↓[31]	No change[144]	No change[145]	↑ activity[147,145] No change[148]
P38	↓[31]	Upregulated[144]	↑ activity[145], No change in activity [143]	↑ activity[145- 148], No change in activity[143]
AKT	↓[31]	Required[33]	↑ activity[149], No change in activity [143]	↑ protein[150], No change in activity[143]
Calcineurin	Unknown	↑[151]	No change[152]	↑ activity[153,154], ↑ protein[150,155]
NFAT	Unknown	No change[154]	No change[156]	↑ activity[18], ↑ protein[157]
UPS				
Ubiquitin	Unknown	Unknown	↑ activity[93]	↑ protein[92,94]
UbB(polyubiquitingene)	Unknown	Unknown	Unknown	↑ mRNA[158]
19S proteolytic subunit	Unknown	Unknown	↑ protein[93]	↑ RPN1 and RPN2 protein[90]
20S proteolytic subunit	Unknown	Unknown	↓ caspase and trypsin activity[93]	↓ mRNA[95,96], ↑ protein[90,159]
26S proteolytic subunit	Unknown	Unknown	↑ activity[93]	↓ activity[94], ↑ protein[94], ↑ mRNA of P40[90], ↑ activity[90]

to normal values by 14 days postpartum [31]. Further studies on the role of ERK in pregnancy are warranted.

P38 MAP kinases

P38 kinases are stress-activated signaling molecules involved in cardioprotection [31, 43, 44]. P38 is well characterized for its role in inflammation [45]. These kinases are thought to be relatively minor players in the hypertrophic process [46]. Deletion of P38 in the heart leads to increased fibrosis, apoptosis, and reduced cardiac function [47]. However, excess P38 activation also has a detrimental effect on the heart leading to pathological heart hypertrophy [43]. Gonzalez *et al.* showed that phospho-P38 levels decreased in late pregnancy and were normalized 14 days postpartum indicating that P38 signalling plays a role in pregnancy-induced cardiac hypertrophy [31].

STAT3

STAT3 signalling mediates hypertrophy and angiogenesis in the heart [48,49]. STAT3 is thought to be a critical factor in mediating cardiac hypertrophy under both pathological and physiological conditions [50]. STAT3 promotes anti-apoptotic signalling; its role in this process has been characterized during cancer [51-53].

STAT3 has been characterized for its role in adverse ECM remodeling and inflammation in the heart during pathological heart hypertrophy. STAT3 signalling seems to play an important

role in preventing inflammation and cardiac fibrosis. Ablation of STAT3 results in higher sensitivity to inflammation, cardiac fibrosis, and heart failure with advanced age [54-56]. Hilfiker-Kleiner *et al.* observed increased STAT3 signaling in the heart during pregnancy [48].

Calcineurin and NFAT

Calcineurin is a calcium dependent phosphatase that activates NFAT downstream. Activation of this signaling pathway is sufficient to generate cardiac hypertrophy, and inhibiting this pathway delays the progression of pathological hypertrophy [57-60]. Nothing is known about calcineurin signaling in the heart during pregnancy.

JNK

JNK is another MAPK subfamily that plays a role in heart hypertrophy. JNK is upregulated rapidly following pressure overload, but is not activated during volume overload [61, 62]. JNK overexpression leads to hypertrophy [63]. JNK seems to be necessary in maintaining cardiac contractility and preventing failure during mechanical overload [43]. This is emphasized by the fact that JNK is associated with some extracellular matrix remodeling, possibly a response to protect contractile function [64, 65]. Gonzalez *et al.* showed decreased phospho-JNK/JNK during pregnancy, which is restored and possibly elevated post-partum [31].

Role of microRNAs in pregnancy-induced cardiac hypertrophy

MicroRNAs are non-coding RNAs that regulate gene expression by blocking transcription or by repressing translation of their target genes [66, 67]. The temporal regulatory role played by Lin-4 and let-7 in controlling the larval development in C. elegans led to the establishment of microRNAs as members of gene regulatory networks [68-71]. Since then, microRNAs have been implicated in almost every aspect of cellular physiology including growth, metabolism, muscle differentiation, stem cell division and apoptosis [72-76]. In the context of cardiac remodeling and hypertrophy, a number of studies have shown the importance of microRNAs in the regulation of gene expression [77, 78]. Cardiac hypertrophy is a complex process that involves change in the composition of ECM such as fibrosis, changes in contractility and fetal gene expression, as well as altered angiogenesis. Depending on the type and extent of the stimulus, these changes are manifested in various forms of physiological and pathological hypertrophy [79]. Emerging evidence shows that various microRNAs modulate key components of hypertrophy. Of interest are miR-1 and miR-133 that regulate growth related genes responsible for cardiac hypertrophy [80, 81]. MiR-208 is involved in myocardial fibrosis and is a positive regulator of fetal gene expression [82]. MiR-27a regulates cardiac contractility by targeting β myosin heavy chain in cardiac myocytes [83]. Cardiac specific overexpression of miR-195 results in dialated cardiomyopathy in mice [78]. However, majority of these microRNAs are involved in pathological cardiac hypertrophy and very few studies have tried to identify signature microRNAs that are differentially regulated in physiological versus pathological hypertrophy. Of note, miR-29 family has been shown to control physiological cardiac hypertrophy in mice during aerobic training [84]. In another setting of physiological hypertrophy wherein pI3K is constitutively active, miR-222, miR-34a and miR-210 have been demonstrated to be differentially regulated in physiological versus pathological hypertrophy [85]. These studies are an important attempt to delineate the mechanisms involved in physiological versus pathological hypertrophy. However, there are no studies to analyze the role of microRNAs in cardiac adaptations to pregnancy. Further studies in microRNA biology are needed for better understanding and design of clinically relevant therapies for cardiovascular complication during pregnancy.

Role of ubiquitin proteasome system in pregnancy-induced cardiac hypertrophy

The heart is the only organ in the body that is constantly bearing a heavy workload and a high metabolic rate. Therefore it is essential that cardiac cells maintain a very efficient and tightly controlled system for removal of misfolded or damaged proteins. The ubiquitin-proteasome system (UPS) is the major machinery for the degradation of damaged and misfolded proteins in the heart [86]. Regulation of the proteasome function may occur through the association of the core 20S proteasomal subunit with different regulatory complexes such as 19S or 11S that affect proteasomal assembly and activity [87,

88]. Generally however, the covalent binding of ubiquitin molecules to the target protein dictates its degradation by the 26S proteasome. Following attachment of ubiquitin molecules to the target proteins, the 19S regulatory subunits recognize the ubiquitin tags and transfer the protein substrates to be degraded in the inner pore of the 20S catalytic core [89]. A large number of reports have highlighted the functional significance of the UPS in heart hypertrophy. As the cardiac muscle hypertrophies, there is an increase in de novo protein synthesis which could potentially lead to more misfolded or abnormal proteins. As such, an increase in proteasomal activity would be needed to clear these aberrant proteins. Indeed, many studies report an increase in the activity of the proteasome in compensated heart hypertrophy induced by trans-aortic constriction both in mouse and canine models [90, 91]. In fact, increased proteasome activity has been suggested to be required for the development of compensated heart hypertrophy [90, 91]. Both trypsin-like activity (β2) and chymotrypsin-like activity (β5) were significantly increased in the subendocardium, which is subjected to the highest level of wall stress in a canine model of left-ventricular hypertrophy [90]. In fact, these studies suggest that activation of the proteasome is indeed a requirement for the development of compensated hypertrophy following pressure-overload. The proteasome inhibitor epoxomicin prevented the development of pre-existing hypertrophy and the further reduction in the ejection fraction [90, 91]. During the progression of compensated heart hypertrophy to cardiac dysfunction, decreased proteasome activities have been shown [92]. In the isoproteranol-induced volume overload hypertrophy model, Drews *et al.* [93] also showed increased 26S proteasome activities and noted a significant decrease in the 20S activities, which were attributed to a switch in proteasome subpopulations. The expression of proteasome subunits has also been conflicting in different models of cardiac hypertrophy and failure. Most reports show an increase in 20S and 26S proteasome expression in different models of cardiomyopathy and hypertrophy [90, 94], while the transcript levels of representative 20S subunits have been shown to be decreased in failing hearts [95, 96]. Since protein ubiquitination is one of the key mechanisms for targeting a peptide to be degraded by the proteasome's proteolytic pathway, proteasomal activity also depends on the levels of peptide ubiquitination. Immunocytochemical experiments previously revealed markedly increased expression levels of ubiquitin in patients with decompensated cardiomyopathy [94], and other studies show a progressive increase in ubiquitin levels 2-4 weeks post transaortic constriction-induced cardiac hypertrophy in mice [92, 90].

During pregnancy as a result of volume-overload, heart develops a physiological heart hypotrophy. However, the precise role of the UPS in physiological heart hypertrophy during pregnancy is not yet known. Unravelling the role of UPS in pregnancy may influence therapeutic strategies for treating pathological heart hypertrophy.

The role of sex hormones in pregnancy-induced heart hypertrophy

Late pregnancy is a high estrogenic state. Estrogen levels in the plasma increase gradually as the pregnancy progresses and peak at the late-pregnant stage (**Table 1**). The cardioprotective action of estrogen has been well documented in many different experimental models of heart disease. In an experimental model of chronic volume overload induced by aortocaval fistula, female rats were reported to be protected as the mortality following 8 weeks of volume overload was 25% in males, whereas only 2% mortality was observed in females [97]. Furthermore, this apparent cardioprotection, which was lost following ovariectomy, was partially restored by estrogen replacement [98, 99]. Estrogen was also effective in male rats in attenuating chronic volume overload induced structural and functional remodeling in the hearts[100]. These findings demonstrate that, in contrast to males, intact, cycling female rats are able to successfully compensate for the increased myocardial stress associated with chronic volume overload and that this cardioprotection is largely due to the action of estrogen. Estrogen is also known to attenuate the development of heart hypotrophy in various animal models. Estrogen also prevents PE-induced cardiomyocyte hypertrophy *in vitro* [101, 102]. Pedram *et al.* recently showed that E2 therapy can directly inhibit the transition of cardiac fibroblast to myofibroblasts *in vitro*, preventing the secretion of fibrosis-inducing signal transduction proteins and many of adverse remodeling proteins [103]. Additionally, E2 treatment has been shown to directly mitigate adverse ECM remodelling in left ventricular hypertrophy and failure by attenuating

altered collagen, and metalloproteinase expression *in vivo* [104]. Prevention of cardiac fibrosis and heart hypertrophy by estrogen during pregnancy could be one of the mechanisms protecting the late pregnant heart from failure.

Testosterone levels are also increased in the plasma during pregnancy [105, 106]. Estrogen and testosterone have been shown to have opposing effects on chronic cardiac remodeling and function in mice with myocardial infarction (MI). Cavasin *et al.*, suggested that estrogen prevents deterioration of cardiac function and remodeling after MI, but testosterone worsens cardiac dysfunction and remodeling and has a pronounced effect when estrogen levels are reduced [107]. Testosterone has also been implicated in causing cardiac hypertrophy. Clinical data suggest an association of increased serum androgens with cardiovascular mortality in females, but not in males. Detrimental effects of testosterone on post-MI remodelling in female rats have been described [108].

Pregnancy-induced cardiovascular complications

Drastic changes that occur during pregnancy in the cardiovascular system are usually well tolerated in healthy women. However, some healthy women without any cardiovascular complication prior to pregnancy could develop some adverse cardiac events, rarely, which could be fatal. Here, we review some of these complications.

Pregnancy-induced hypertension (preeclampsia) and eclampsia

The blood pressure in healthy pregnant women usually decreases during the second trimester but returns to normal toward the end of pregnancy. Pregnancy-induced hypertension (PIH) or preeclampsia is a medical condition in which the healthy pregnant women start to develop high blood pressure after the 20th week of pregnancy. Severe preeclampsia could lead to dangerous seizure known as eclampsia. Pregnant women with chronic hypertension, multiple gestations, a family history or a previous history of preeclampsia, age under 20 years or over 35 years, obesity or African American ethnicity are at higher risk of developing preeclampsia [109-111]. Although preeclampsia occurs in ~10% of pregnancies and is a life-threatening disease affecting mother and the newborn, the mechanisms underlying the development of preeclampsia are not well known.

During the implantation process, insufficient placental circulation is associated with pregnancy-induced hypertension. This poor circulation produces pro-inflammatory molecules which cause injury to the mother's endothelial cells and result in increased vascular resistance [112]. A functional imbalance between thromboxane A2 (TXA2) and prostacyclin production has been shown to play a role in the development of preeclampsia. Neurokinin-B with the help of TXA2 may play some role in impaired placental neovascularization and down-regulation of vascular endothelial growth factor (VEGF)-mediated signalling [112]. In late pregnancy the placenta secretes VEGF inhibitors like soluble FLT (sFLT), that create an antiangiogenic environment, which is more pronounced in pre-eclampsia and in multiple pregnancies [113]. Suppression of VEGF activity by sFLT in pre-eclampsia impaires diastolic relaxation [113].

Neurokinin-B is found in higher concentration in pregnant women with preeclampsia. The components of renin-angiotensin system (RAS) which have been shown to be increased in healthy pregnancy, are decreased in pregnancy-induced hypertensive mothers [112, 114]. Immunologic mechanisms and aberrations of the RAS have been long considered contributors to the disorder. Bridging these two concepts, numerous studies report the presence of the angiotensin II type I receptor agonist autoantibody (AT(1)-AA) in preeclamptic women. This autoantibody induces many key features of the disorder through AT(1) receptor signaling, and has been implicated in the pathogenesis of preeclampsia. Takimoto and colleagues mated female mice expressing human angiotensinogen with male mice expressing human rennin. Pregnant females displayed transient elevations in blood pressure [115]. In another study, IgG from preeclamptic women was injected into pregnant mice, inducing endothelin-1 (ET-1) by AT(1) receptor activation. They showed that tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) contribute to a signaling pathway which ultimately leads to increased ET-1 production by AT (1) receptor agonist autoantibody action [116].

Peripartum cardiomyopathy

Healthy women may develop peripartum cardiomyopathy (PPCM), a life-threatening disease of

unknown cause, during the last month of pregnancy up to 5 months after delivery. PPCM is characterized by left ventricular systolic dysfunction as a result of dilated cardiomyopathy. PPCM is more common in pregnant women after age 30 and obesity, smoking, alcoholism, African American race, are some of the risk factors [117]. Some possible causes include myocarditis, cardiotrophic viral infection, apoptosis, inflammation and chimerism [118].

Experimental model of PPCM has identified several proteins which play a key role in the development of PPCM. Among them signal transducer and activator of transcription factor-3 (STAT3) has received a lot of attention. STAT3 has been shown to be necessary for protecting mice against PPCM, as female mice with a cardiomyocytes-specific deletion of STAT3 developed postpartum cardiomyopathy with a very high mortality rate [48]. The levels of STAT3 protein have also been shown to be reduced in PPCM patients. STAT3-KO mice also show higher expression of cardiac cathepsin D which cleaves full length prolactin to a subisoform of 16-kDa prolactin [48]. Serum levels of activated cardiac cathepsin D and cleaved prolactin are elevated in PPCM patients. This cleaved form of prolactin is a potent anti-angiogenic, pro-apoptotic and pro-inflammatory substance. The anti-angiogenic property of prolactin disrupts the cardiac capillary network which is known to play a major role in the transition of compensated hypertrophy to failure. In addition, unbalanced peri/postpartum oxidative stress associated with the proteolytic cleavage of prolactin into 16Kda subform has also been speculated as a potential mechanism for the development of PPCM. The fact that bromocriptine, an inhibitor of prolactin release, prevents the development of PPCM, highlights the role of prolactin as a new therapeutic target in peripartum cardiomyopathy [48, 119]. Apoptosis has been shown to play a key role in the development of PPCM. Higher plasma levels of Fas, a cell surface protein that plays essential role in apoptosis, have been reported in some PPCM patients [120]. Inhibition of apoptosis in cardiomyocytes by caspase inhibitor in a mouse model of lethal peripartum cardiomyopathy (Gαq overexpression), abolished the PPCM mortality in these mice [121]. Recent study showed that PPCM is associated with imbalances in angiogenic signalling, and that anti-angiogenic states such as pre-eclampsia or multiple gestation substantially worsen the severity of the disease [113].

Conclusions

Pregnancy-induced heart hypertrophy differs from pathological hypertrophy, as well as physiological hypertrophy during exercise. Further studies are required to identify the role of ubiquitin-proteasome system as well as the key micro-RNAs regulating gene expression in this unique model of physiological heart hypertrophy. The function of the late pregnant heart seems to be preserved under physiological conditions and the drastic hemodynamic changes that occur during pregnancy are usually well tolerated in healthy women. However, some healthy women without any cardiovascular complication prior to pregnancy could develop some adverse cardiac events which, rarely, could prove to be fatal. Therefore these hearts appear to be at a threshold and any additional stress stimuli such as hypertension could drastically deteriorate their function. Management of these life-threatening circumstances and the procurement of women's well-being during pregnancy and postpartum period require a better understanding of the basic molecular mechanisms underlying the remodeling of the heart during this reproductive stage. This review calls for more research in this under explored area that should set the basis for a better treatment of women during pregnancy. Special emphasis has to be given to the guidelines on disease management in pregnancy [122].

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