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REVIEW

Role of pregnancy hormones and hormonal interaction on the maternal cardiovascular system: a literature review

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Abstract
Hormones have a vital duty in the conservation of physiological cardiovascular function during pregnancy. Alterations in oestrogen, progesterone and prolactin levels are associated with changes in the cardiovascular system to support the growing foetus and counteract pregnancy stresses. Pregnancy hormones are, however, also linked to numerous pathophysiological outcomes on the cardiovascular system. The expression and effects of the three main pregnancy hormones (oestrogen, prolactin and progesterone) vary depending on the gestation period. However, the reaction of a target cell also depends on the abundance of hormone receptors and impacts put forth by other hormones. Hormonal interaction may be synergistic, antagonistic or permissive. It is crucial to explore the cross talk of pregnancy hormones during gestation, as this may have a greater impact on the overall changes to the cardiovascular system.

Keywords Pregnancy · Hormones · Physiology of pregnancy · Prolactin · PPCM

Introduction

Pregnancy is accompanied by significant changes in the hormonal milieu [1]. Hormones play a major role in molecular and physical changes that are observed in maternal cardiovascular adaptations during pregnancy [2]. When well regulated, hormones maintain a physiological adaptation to the cardiovascular system [3]. However, hormonal imbalance can also trigger pathological changes that may be fatal to the maternal cardiovascular system [4, 5]. It is also important to consider hormonal interactions which may alter the individual hormone's impact. This literature review aims to explore the benefits and risks of individual pregnancy hormones, as well as their cross talks and interactions. A few reports have outlined the presence of hormonal interaction; however, the impact of these interactions on the cardiovascular system is not clear.

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Physiological changes of the cardiovascular system during pregnancy

Alterations in the cardiovascular system in pregnancy begin early in the first trimester (Table 1) in that, by 8 weeks, the cardiac output would have increased by 20% [2]. The initial change is probably peripheral vasodilatation, which leads to falling systemic vascular resistance (SVR) [6]. Heart rate rises as a compensatory response to falling SVR [6], it surges throughout gestation by 10–20 bpm, peaks in the last 3 months [3] and then yields to preconception levels within 10 days postpartum [7].

A recent meta-analysis study on cardiac output and haemodynamic changes during pregnancy confirmed that cardiac output also upturns during pregnancy, reaching its peak in the early third trimester [8]. Unlike heart rate, cardiac output follows a non-linear array of adaptation. Initially, it is alleged to be facilitated by increases in stroke volume, whereas, later, the increase is linked to heart rate [9, 10]. Stroke volume escalates gradually up to the second trimester and then stabilises or decreases late in the third trimester [11]. It then returns to non-pregnant values soon after delivery [2].

Table 1 Physiological changes of the cardiovascular system during pregnancy

Physiological Condition	During gestation			Postpartum	
	1st trimester	2nd trimester	3rd trimester	Early (0-2 mnths)	Late (2-6 mnths)
Vascular resistance	↓	↓	↑	↓	↓
Heart rate	↑	↑	↑	Remains high as in pregnancy	↓
Cardiac output	↑	↑	Minimal increases	↓	↓
Myocardial contractility	↓ [12] no difference [13]. ↑ [14]	↓ [14]	↑	↑	↓
Left ventricular volume	↑	↑	↑	↓	↓
Left atrial volume	↑	↑	↑	↓	↓
Left ventricular mass	↑	↑	↑	↓	↓
Ejection fraction	↑ [15]	No change[16] ↓ [17]	No change[16] ↓[17]	↓	↓

Hemodynamic changes

The maternal cardiovascular system goes through progressive adaptations during pregnancy to support the mother and the growing foetus. These changes include increased circulating blood volume [12], reduced vascular resistance [13] and increased cardiac output [14]. Table 1 summarises some of the hemodynamic and physical changes in the cardiovascular system during pregnancy and postpartum.

Hemodynamic changes during pregnancy also cause blood pressure (BP) instabilities [15]. There are disparities on the normal alterations in uncomplicated pregnancies. However, in several studies where the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (NHBPEPWG) recommendations [16] were used to measure BP, systolic blood pressure (SBP) remained unchanged, whilst diastolic blood pressure (DBP) and mean atrial pressure (MAP) dropped up to 26–28 weeks [7, 17]. Thereafter, DBP and MAP rose towards term [7, 17].

Conflicting results have been reported on cardiac contractility during the first trimester of pregnancy. George et al. reported enhanced intrinsic contractility [13], whilst other studies have reported no change [3, 18], or decreased contractility [14] in the same phase of pregnancy.

Studies also reported either no change, or a significant increase, in the cross-sectional area of left ventricular outflow tract [3, 9]. The left atrial enlarges slowly, beginning at 5 weeks, and plateauing at 28–34 weeks [19, 20]. However, ventricular ejection fraction seems stable during the course of pregnancy [3].

Structural and extracellular matrix remodelling

Structural modifications within the heart reflect increased volume load related to pregnancy and cause dilatation of the valve ring and foster myocardial thickness (cardiac hypertrophy) [20]. Heart hypertrophy is either physiological and adaptive, or pathological, which is maladaptive [21]. Cardiac hypertrophy induced by pregnancy is a temporary revocable development of increased left-side chambers and myocyte dimension [1]. However, postpartum resolution of the ventricular hypertrophy seems to take longer (approximately > 6 weeks after birth) than the rest of the prepartum changes [9].

Pregnancy-induced cardiovascular complications

Pregnancy hemodynamic and hormonal changes are usually well tolerated in healthy mothers [22]. However, cardiovascular complications may develop in some women who did not have any preceding adverse cardiac history before pregnancy [23, 24]. Approximately, 1% of pregnant women are estimated to acquire cardiac disease during pregnancy, which can have a significant effect on both maternal and foetal outcomes [25–27]. These events, even if they are rare, could be fatal. Some of the complications include pathological cardiac hypertrophy [28], pregnancy-induced hypertensive disorder [23, 24], peripartum cardiomyopathy (PPCM) and several metabolic complications [10, 29].

South Africa recorded a constant increase in institutional maternal mortality rate (iMMR) for cardiovascular diseases, from 3.73 per 100,000 in 2005–2007 to 6 per 100,000 in 2011–2013 [30, 31]. iMMR due to cardiac disease in maternity in Africa is mostly dominated by PPCM (34%) and rheumatic heart disease (25.3%) [30]. In the United States, overall cardiovascular disease contributes to approximately 33% of maternal deaths during pregnancy [27].

Pathological cardiac hypertrophy

A pathological stimulus caused by pressure overload gives rise to concentric hypertrophy characterised by thick walls and dense myocardium [28, 32]. However, volume overload results in eccentric hypertrophy due to an increase in diastolic wall stress [32]. Eccentric hypertrophy is identified by large dilated ventricles and a relatively thin myocardium wall [32, 33]. These events can lead to cardiomyopathies and heart failure.

Gestational hypertension and pre-eclampsia/eclampsia

Pregnancy-induced hypertension (PIH) is the occurrence of new hypertension after 20 weeks gestation, in the absence of proteinuria or pre-eclampsia (PE) [34]. PE is identified when a woman with gestational hypertension also has elevated protein excretion in urine. Eclampsia is a severe complication of PE which is often accompanied with seizures [24].

PIH is deemed to be caused by many factors such as cardiovascular maladaptation, vasoconstriction, genetic predisposition, immunologic intolerance between feto-placental and maternal tissue, platelet activation and vascular endothelial dysfunction [34]. The presence of metabolic aspects, hyperlipidaemia and insulin resistance are also linked with PE [35].

Peripartum cardiomyopathy

PPCM is a disease identified by the occurrence of systolic heart failure in the ninth month of pregnancy, or in the first 5 months post-delivery in previously healthy women [36]. The pathophysiology of PPCM is still largely unknown, although numerous hypotheses including viral myocarditis, foetal microchimerism, malnutrition, hemodynamic stress of pregnancy, autoimmune processes, inflammatory factors, and low selenium levels have been implicated [37, 38].

A shift in the angiogenic balance toward an antiangiogenic environment has emerged as the strongest driving factor of PPCM [36, 39]. Findings in 2007 by Hilfiker-Kleiner et al. have demonstrated that PPCM is triggered by the swiftly shifting hormonal milieu of late gestation, leading to vasculopathy in susceptible women [40]. The antiangiogenic prolactin (16 kD) and sFLT1 are the major contributors [40].

The 16-kDa prolactin fragment is produced by digestion of the full-length prolactin (23 kDa) with proteolytic enzymes such as cathepsin D and matrix metalloproteinases (MMP) [40]. The increase of 16-kDa PRL level observed in PPCM patients has been associated with low activation of the signal transducer and activator of transcription 3 (STAT3) and the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [41]. Reduced level of STAT 3 and PGC1-α further increases the activity of MMP and cathepsin D [38]. 16-kDa PRL also directly impairs endothelial function and triggers the release of micro-RNA 146a, which in turn has detrimental effects on cardiomyocytes [42].

Diagnosis of PPCM

Presenting symptoms in PPCM patients are highly variable but may include fatigue, dyspnea, orthopnea, peripheral edema, palpitations, chest pain, decreased exercise tolerance, and abdominal discomfort due to passive congestion of the liver [43, 44]. Most of these symptoms overlap with normal physiological symptoms of pregnancy hence the diagnosis is based on suspicion.

PPCM is considered to be a diagnosis of exclusion [37], a thorough evaluation is necessary to eliminate other potential cardiac and non-cardiac explanations for the patient's clinical presentation. The requirements for diagnosis of PPCM include clinical signs of heart failure and an echocardiographic left ventricular ejection fraction (LVEF) of $\leq 45\%$, ECG, and magnetic resolution imaging (MRI).

Laboratory measurements of NT-proBNP and right ventricular (RV) dysfunction may be measured as a predictor of outcome [37]. A recent study by Haghikia et al. confirmed the use of RV dysfunction to predict adverse outcome in PPCM [45]. Reduced RVEF at initial presentation in this study was associated with a lower rate of full cardiac recovery [45].

Management of PPCM

Management is targeted, as with other cardiomyopathies, on managing volume status, neutralising neurohormonal maladaptive responses, and preventing complications [46]. Patients presenting with acute severe heart failure symptoms require prompt treatment in an intensive care unit. However, because of the high rate of recovery in PPCM, early implantation of a permanent implantable cardioverter defibrillator should be avoided, and wearable cardiac defibrillators are often used instead [46, 47].

If PPCM presents during pregnancy diuretics to reduce preload and treat edema, vasodilators (hydralazine) to

increase cardiac output and stroke volume, and decrease vascular resistance, as well as beta-blockers are often administered [37, 48]. However, dehydration-induced hypoperfusion and lower foetal birth weight should be monitored in patients under treatment.

For PPCM that present postpartum neurohormonal blockade with angiotensin-converting enzyme inhibition, angiotensin receptor blockers, and mineralo-corticoid receptor blockers are considered as first-line heart failure medication according to standard heart failure guidelines [47, 48]. Recent reports have found that the use of bromocriptine, a drug inhibiting prolactin may be beneficial in patients with acute-onset PPCM [45]. All patients receiving bromocriptine should receive standard heart failure therapy with at least prophylactic anticoagulation.

Thromboembolism is often a complication in PPCM patients due to pregnant women having increased levels of coagulation factors VII, VIII, and X, and plasma fibrinogen during late pregnancy and up to 4–6 weeks postpartum [49]. A depressed LV function and hypercoagulable state cause a higher incidence (17%) of LV thrombus [49]. The American Heart Association, American College of Cardiology guidelines and European Society of Cardiology all support the use of anticoagulation resulting from a hypercoagulable state during pregnancy in patients with PPCM and severe LV dysfunction (LVEF < 30%) [49]. Another recent study investigating pregnancy outcome after exposure to the oral anticoagulant rivaroxaban in women at suspected risk for thromboembolic events gave reassurance to those women, who were inadvertently exposed to rivaroxaban in early pregnancy [50].

Sudden cardiac death has been reported in PPCM patients with sustained ventricular arrhythmias. A recent study underpins the elevated risk for ventricular tachyarrhythmias in patients with newly diagnosed PPCM and reduced LVEF [51]. Patients with sustained ventricular arrhythmias or history of sudden cardiac death in the acute setting may be candidates for a wearable cardioverter/defibrillator (WCD) [37, 51]. The use of implantable cardiac defibrillator (ICD) is another alternative; however, this option should be weighed as often PPCM patients recover cardiac function in 6 months [37].

Pregnancy-induced metabolic complications

Gestational diabetes mellitus (GDM) or hyperglycemia during pregnancy may lead to cardiovascular disease [24]. GDM is a form of Type 2 diabetic mellitus (T2DM), characterised by glucose intolerance of different levels established for the first time during pregnancy [52]. GDM possesses subsequent cardiovascular risks similar to those which build up in the non-pregnant female population once T2DM develops [52]. Studies have shown that diabetic patients have a two- to fourfold susceptibility to coronary artery disease (CAD) and myocardial infarction (MI) [53, 54]. Hence, a systematic dissection of the metabolic transformations arising during pregnancy, and in the subsequent years, provides an exceptional opportunity to find new biomarkers for better long-term outcomes, mainly to decrease cardiovascular risk [52].

Persistence of weight gain after pregnancy

Pregnancy is the only conventional physiological condition whereby the body gains more than 20% weight within 9 months [55]. Lactation increases the maternal ability to restore normal weight [55]. However, it can be hindered by lifestyle factors such as limited exercise, diet and inadequate sleep [55]. Kew et al. noted that an adverse cardiometabolic profile commences early in the first year if weight is not lost between 3 and 12 months after delivery [56].

Hormonal changes during pregnancy

Modifications of maternal endocrine and metabolic homeostasis are key for a successful pregnancy [57]. The hypothalamus, pituitary gland and the placenta add to the endocrine adaptations to pregnancy by producing numerous hormones [58]. Well-studied hormones that have a direct impact to the cardiovascular system include oestrogen, prolactin and progesterone. The levels are very dynamic during gestation and postpartum, and are critical in conserving the cardiovascular adaptations. Figure 1 is a schematic diagram which shows the changes of female hormones during pregnancy.

Oestrogen and progesterone levels increase steadily during pregnancy, attain their peak in the last trimester and drop soon after labour—as illustrated in Fig. 1. Oestrogen and progesterone are both produced in the corpus luteum during the first 10 weeks of gestation and, soon after implantation, the placenta takes over [59, 60]. In the third trimester, progesterone levels range from 100 to 200 ng/ml and the placenta secretes about 250 mg/day [60]. However, the placenta lacks the required enzymes to manufacture oestrogens from cholesterol or progesterone. To bypass this shortfall, dehydroisoandrosterone sulfate (DHA) from the foetal adrenal is processed to estradiol-17β by the trophoblasts.

Prolactin is secreted by the anterior pituitary gland in response to suckling stimulus of young mammals. The prolactin concentration increases during pregnancy so that, by the end of gestation, levels are 10–20 times higher than non-pregnant levels [60]. The increase in prolactin is most likely induced by increased estradiol concentrations during pregnancy [61]. However, its actions are antagonised by the presence of progesterone [62]. Following reduction of progesterone and oestrogen levels at parturition, copious

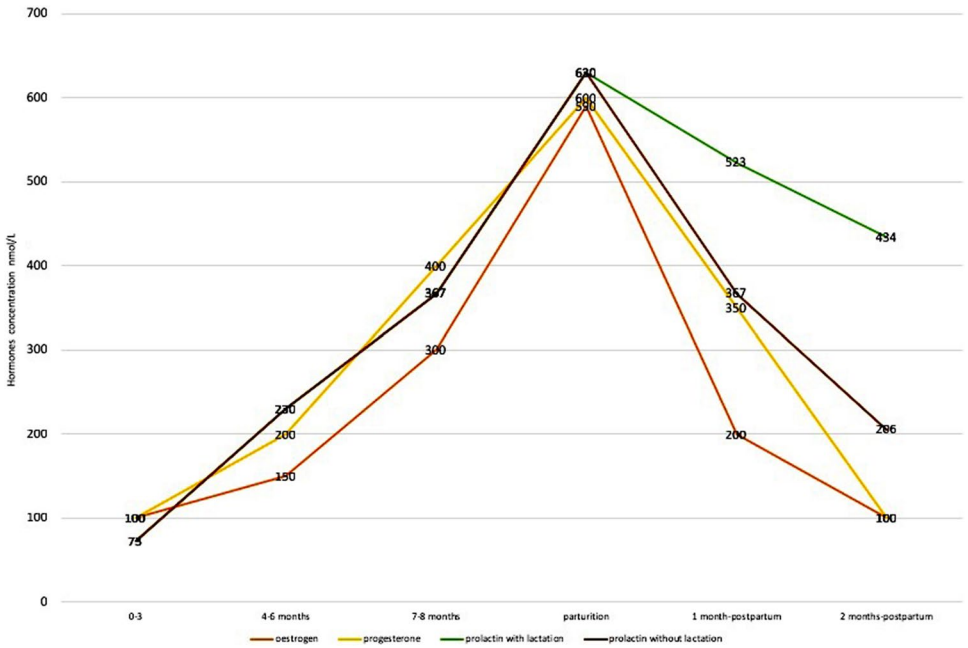

Fig. 1 Changes of hormones level during pregnancy and postpartum. Pregnancy hormones increase gradually from day 1 of pregnancy to birth. After birth most of the hormones start to revert back to normal levels. However, if there is lactation, prolactin levels remains high due to periodic stimulation

milk secretion begins [62]. Postpartum, throughout lactation, women respond with a dramatic elevation of prolactin levels during the suckling stimulation [63]. However, if the woman does not breastfeed, prolactin returns to normal levels within 2–3 weeks after delivery (Fig. 1).

Oestrogen

Oestrogens are a group of steroid hormones that are secreted by the ovaries and the placenta during pregnancy [64]. However, oestrogens can also be secreted by other non-reproductive tissues such as the liver, heart, muscle, bone and brain [65].

E2 is the predominant form and is involved in numerous physiological processes. E1 is secreted mainly after menopause and E3 is secreted by the placenta during pregnancy.

There are three major types of oestrogens known as estradiol, estrone, and estriol [66]. Estrone and estradiol are synthesised by the aromatisation of androstenedione and testosterone, respectively and estriol is synthesised from estrone [66]. E2 is the highly potent oestrogen secreted during the premenopausal period, whereas E1 is important after menopause, when it is synthesised from adrenal dehydroepiandrosterone in the adipose tissue [65]. E3 is the least abundant and it is formed by the placenta from E1 through 16α-hydroxylation [65].

When oestrogens are secreted into the blood stream, they affect numerous target cells which express oestrogen receptors. Several cells such as the endothelium, epithelium, muscle, bone, cartilage, hematopoietic cells, neurons and glia have oestrogen receptors. However, oestrogens can also operate in the paracrine and autocrine systems.

Physiological function of oestrogens on the cardiovascular system

Oestrogens have pleiotropic effects on the cardiovascular system. It controls vascular function [67, 68], inflammatory response [69], metabolism [10], insulin sensitivity [10], cardiac myocyte survival [70], mitochondrial function [71], development of hypertrophy [72] and ultimately cardioprotection [73, 74].

Oestrogen and endothelial function Vasculature provides sufficient perfusion of the maternal–foetal interface which is critical during pregnancy [75]. Oestrogens help to maintain efficient vascular adaptations during pregnancy [68].

In a rat model, new production of oestrogen during decidualisation assisted in angiogenesis at the implantation site and helped in maintaining early pregnancy [76]. As gestation progresses, oestrogens exert profound multifaceted protective effects on the vasculature [77]. Oestrogen has a direct effect on the endothelium and vascular smooth muscle, through both rapid signalling pathways and genomic mechanisms [78]. Cellular and animal studies have suggested generation of nitric oxide (NO) and prostacyclins, as potential benefits of oestrogen on the endothelium-mediating vasorelaxation, promoting endothelial repair and regeneration, with anti-inflammatory and antioxidant effects [79–83].

Oestrogen and cardiac hypertrophy Cardiac hypertrophy during pregnancy is influenced by adjustments in the signalling pathways, extracellular matrix and the levels of hormones [23]. Oestrogen can slow the development of hypertrophy by modulating several pathways of cardiac

hypertrophy [84–86]. The alleged molecular mechanisms involve calcineurin degradation [87], mammalian target of rapamycin signalling [88], control of phosphorylated p38 mitogen-activated protein kinase (MAPK) pathways [86] and regulation of cardiomyocyte histone deacetylases [89].

However, oestrogen was also found to exert pro- and anti-hypertrophic effects in vitro, dependent of its concentration [90]. A hypertrophic effect was observed at lower concentration and an anti-hypertrophic effect at higher concentration [90]. The hypertrophic effect of E2 is facilitated by raised ERK activation [85]. The mechanisms underlying the anti-hypertrophic effect of higher concentrations indicate its inhibitory effect on calcineurin via stimulation of myocyte-enriched calcineurin-interacting protein 1 [84, 91].

Oestrogen and cardiac oxidative stress E2 also improves the defence against oxidative stress in endothelial cells and cardiomyocytes [92, 93]. Often oxidative stress correlates to cardiomyocyte apoptosis and cardiac contractility [70, 94]. Several signalling pathways have been implicated to the E2 inhibition of myocyte apoptosis [95]. These consist of inhibition of NF-kB [96], stimulation of phosphoinositide-3 kinase/Akt signalling [97], prevention of apoptosis signal-regulating kinase 1 (ASK1) activity [98] and promotion of p38β activity, which cause inhibition of p53 and, later, improvement of mitochondrial redox response [99].

Oestrogens also defend against apoptosis of endothelial cells (ECs) [100, 101]. Dose-dependent treatment with E2 resulted in receptor-mediated inhibition of TNF-α-induced endothelial cell apoptosis [100]. This also preserved endothelial integrity and maintained functionality after noxious stimuli [100].

Mechanism of oestrogen function

Genomic oestrogen mechanism The mechanism of oestrogen action can be grouped into two classes—the genomic or classical pathway and the rapid non-genomic pathway (Fig. 3). The classical pathway of oestrogen action is dependent on two oestrogen receptors (ERs), ERα and ERβ, which act as transcription factors [72, 95, 102]. These two receptors are primarily found in the cytoplasm and they migrate into the nucleus after binding to E2 [103, 104]. In humans, ERα is encoded by *ESR1* gene whilst *ESR2* encodes ERβ [102].

ERs are members of the nuclear receptor superfamily [105]. They positively regulate gene expression by binding to target gene oestrogen response elements (EREs), changing the binding of other transcription factors and gathering co-activators to the transcriptosome [105]. Figure 2 illustrates the classical hormone/receptor paradigm. This involves ER monomers in the cytosol that make protein complexes with chaperone heat-shock proteins (HSP) [102]. When the ER–HSP complex binds with E2, the HSP dissociate leaves only ER–E2 monomers [102]. These ER–E2 monomers then dimerize, forming mainly homodimers [102]. However, ERα/ERβ heterodimers have also been detected [106]. ER dimers can bind directly to DNA via oestrogen response elements (ERE) in the promoter of target genes, or indirectly, through protein–protein tethering [105, 107]. This regulates a host of gene transcriptions, depending on the cell type, the presence of transcriptional cofactors, the type and concentration of the ligand, and the type of ER dimer formed [69].

Non-genomic oestrogen mechanism Nevertheless, numerous experimental studies also indicate the existence of a non-classical mechanism of steroid action. G-protein oestrogen receptor (GPER) is the main mediator of the rapid effects of oestrogens via non-classical receptor systems [69, 108, 109]. The localization of GPER has been the subject of controversy. Some authors have described it as associated with plasma membrane, while others suggested the endoplasmic reticulum [108, 110].

GPER also plays a part in regulating physiological vascular and myocardial functions [111, 112]. It is expressed in both endothelial and smooth muscle cells in the entire cardiovascular system [111]. Activation of GPER by oestrogens stimulates a number of signalling cascades, including mitogen-activated protein (MAP) kinase family members (e.g., extracellular signal-related kinase 1/2; ERK1/2), activation of phosphatidylinositol-3-kinase (PI3K), generation of cAMP, and calcium mobilisation [111, 113].

Progesterone

High amounts of progesterone are secreted by the corpus luteum and small amounts by the adrenal glands [110, 114]. During human pregnancy, initial supply of progesterone is from the corpus luteum and then, after the 8th week, the production shifts to the placenta [60]. The placenta uses cholesterol as the initial substrate to manufacture progesterone [115]. Most of the produced progesterone enters the maternal circulation, but minute quantities diffuse across the placenta into the foetal circulation.

Physiological function of progesterone on the cardiovascular system

Progesterone induces a number of physiologic and protective effects on the cardiovascular system, such as an increase in blood volume [116], vasodilation [117] and cardiomyocytes protection against apoptosis [118].

Progesterone induces vasodilation Progesterone promotes vasodilation due to its effect on the function of eNOS by both genomic and non-genomic mechanisms

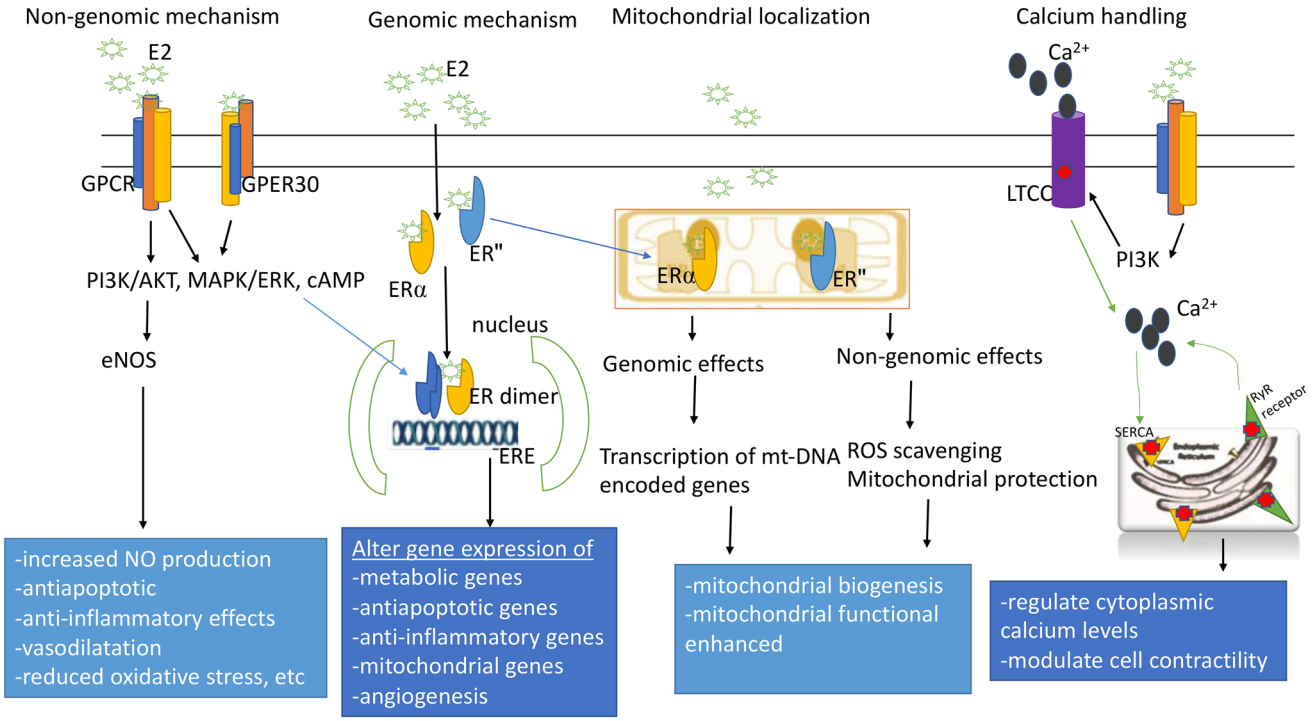

Fig. 2 Genomic and non-genomic effects of oestrogen on cardiac cells. Increase in phosphoinositide/AKT (PI3K/AKT) in the non-genomic signalling increases endothelial nitric oxide synthase (eNOS). Endothelial nitric oxide (eNO) relapses in blood vessels. Oestrogen inhibits cardiac fibrosis by increasing cyclic adenosine monophosphate/PKA (cAMP/PKA) block endothelin 1 (ET1) and transforming growth factor (TGFβ)-dependent cardiac hypertrophy and fibrosis. Genomic response also activates eNOS gene expression and numerous other genes involved during myocardial remodelling. Oestrogen has been shown to increase the electron transport chain activity and prevent the production of reactive oxygen species (ROS) in the mitochondria. It modulates the mitochondrial function through both genomic and non-genomic mechanisms. Oestrogen also modulates cell contractility by regulating calcium ion levels in the cytosol through non-genomic mechanism. Oestrogen binds directly to proteins such as the L-type calcium channels (LTCC), ryanodine receptor (RyR) or the SERCA. Oestrogen can also modulate cell contractility indirectly by producing PI3K which modulates LTCC. Mark proteins that directly bind oestrogen and modulate calcium handling

[119, 120]. Progesterone activates PI3K/Akt which then phosphorylates eNOS at serine 1177 (Ser1177-P-eNOS) [121, 122]. An increase of eNOS causes augmented NO production which changes the vascular tone and increases blood flow [123]. It also help in the balancing of the profound changes in electrolyte during physiological pregnancy [124].

Progesterone protects against apoptosis Progesterone was also found to protect cardiomyocytes from apoptotic cell death [118, 125]. In experimental studies using doxorubicin (Dox) to induce apoptosis, progesterone inhibited apoptosis in a dose- and time-dependent manner [118, 125]. Progesterone induces the expression of anti-apoptotic gene *Bcl-xL* [118]. Progesterone also induces transcription of several other genes such as *metallothionein I* [118]. Metallothionein I is an antioxidant metal-binding protein and also has cytoprotective effects [118].

Pathophysiological effect of progesterone during pregnancy

Several studies have shown that elevated levels of progesterone are associated with increased pathological effects in both men and women [126, 127]. The normal range of

Table 2 Reference ranges for progesterone in women at different stages of life

Life category	Reference range (ng/mL)
Early stage of menstrual cycle	< 1
Middle stage of menstrual cycle	5–20
Postmenopausal stage	< 1
Pregnancy	
First trimester	11.2–90
Second trimester	25.6–89.4
Third trimester	42.5–48.4

progesterone which varies greatly in women at different stages of life is summarised in Table 2.

High progesterone levels may promote upregulation of angiotensin I (Ang I) mRNA [128]. Subsequently, Ang I is cleaved by the ACE (angiotensin-converting enzyme) generating Ang II. ACE/Ang II causes vasoconstriction, inflammation, fibrosis, cellular growth and fluid retention [128]. This was also proved in an animal model study involving progesterone treatment, which demonstrated that high levels of progesterone are associated with a rapid decrease in vasodilation and blood pressure [124].

Increased serum progesterone levels have also been associated with increases in CD36 (cluster of differentiation 36) levels [129]. CD36 is a receptor for uptake of oxidised LDL (oxLDL) by monocytes/macrophages. This plays a prominent part in the formation of atherosclerotic lesions [129].

Progesterone also has a robust non-genomic effect on cardiac ion channels [130]. Exposure to small amounts of progesterone (100–1000 nM) decreases action potential duration (APD) and affects ventricular muscle contraction [126]. Progesterone attenuates and slows cardiomyocyte contraction, with calcium transients in males but not in females [126]. Additionally, progesterone (from 10-7M to 10-5M) has been shown to reduce Ca^{2+} uptake in the isolated papillary muscle of rabbit and guinea pig hearts [127].

Mechanisms of progesterone

The effects of progesterone are mediated by genomic (nuclear) and non-genomic (extranuclear) receptor mechanisms (Fig. 3) [131]. Progesterone is a lipophilic molecule which, during the genomic mechanism, diffuses into the cytoplasm where it interacts with two specific nuclear progesterone receptors (PRs), namely PR-A and PR-B. During physiological conditions, PR-A and PR-B are equally expressed in cardiomyocytes and other cells [131]. However, a third type, PR-C, is more abundant in myometrial tissue [132].

Upon binding to progesterone both isoforms of nuclear PR change shape. The receptors then homo- or hetero-dimerize and bind to hormone response elements (HRE) in the promoter regions of target genes [122]. In addition, PRs also act together with co-activators, co-repressors and transcription factors [133].

Progesterone also applies rapid non-classical effects on various signalling pathways, independent of transcriptional or genomic regulation [134]. This non-genomic mechanism is facilitated by membrane-bound PR (mPR) [135]. New data presented show that mPRα, mPRβ and mPRγ are also present in human endothelial and smooth muscle vascular cells [136]. Non-genomic effect of progesterone involves the rapid activation of MAPK signalling and intracellular Ca^{2+} increase [137]. Direct instant progesterone actions were

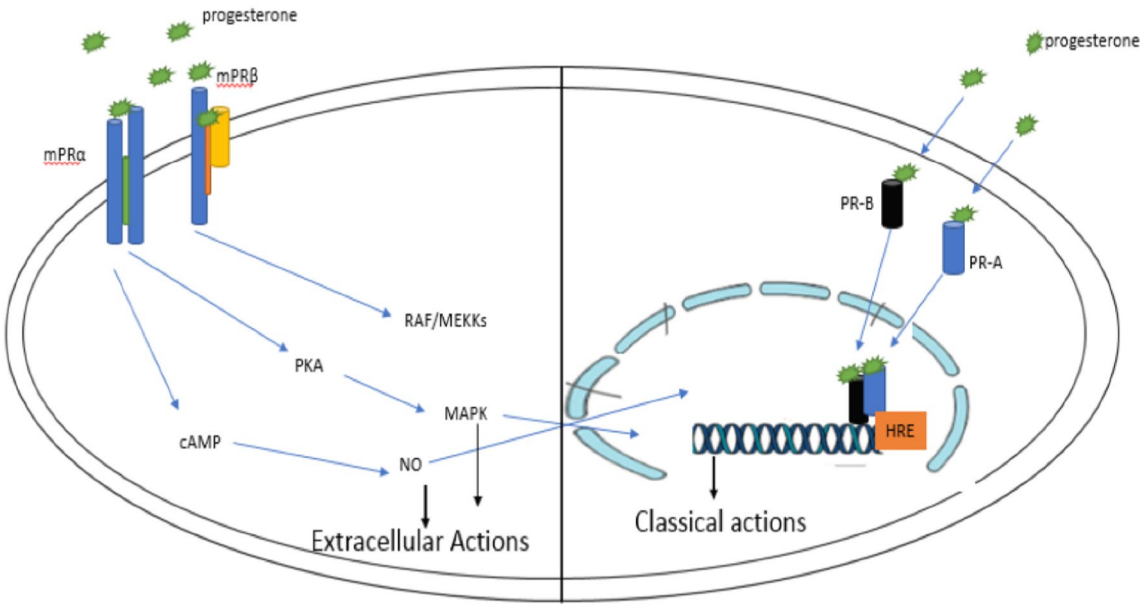

Fig. 3 Classical and non-genomic mechanism of progesterone. Progesterone activates the non-genomic pathway through membrane-bound receptors (mPRα, mPRβ and mPRγ). This rapid pathway elicits the activation of cyclic adenosine monophosphate (cAMP) and mitogenic-activated protein kinase (MAPK) pathways which, through other downstream pathways, produce the extranuclear actions of progesterone. The non-genomic and genomic pathways can also be overlapping with MAPK and nitric oxide (NO), influencing the expression of other genes. The genomic mechanism is facilitated by PR-A and PR-B which receive progesterone in the cytosol. The receptors dimerise and enter the nucleus

reported in humans and mammalian vascular smooth muscle cells causing a rapid influx of calcium [136].

Prolactin

Prolactin (PRL), also known as luteotropic hormone, is mainly involved in milk production in mammals [138]. During pregnancy, prolactin concentration increases after 6 weeks and reaches the highest level in late pregnancy [139]. The most abundant form of prolactin is the 23-kDa PRL which is secreted by the pituitary gland. However, the 23-kDa PRL can be spliced into smaller variants [140, 141].

Physiological function of prolactin

Prolactin is a multifunctional hormone whose receptors are expressed in almost all organs of the human body which, in turn, enables it to influence multiple physiological processes, including endocrine and cardiovascular properties [142, 143]. The major isoform, 23-kDa prolactin has proangiogenic activity and reportedly stimulates endothelial cell (EC) proliferation [138]. The first study to demonstrate that prolactin can stimulate the angiogenic process was conducted in bovine pulmonary artery endothelial cells, using rhodamine-labelled prolactin. The investigations observed specific prolactin uptake, indicating the presence of a prolactin receptor [144]. When the same endothelial cells were mechanically wounded and treated straight way with high prolactin doses between 62.5 and 1000 ng/mL, the cells differentiated and had reduced f-actin staining in comparison with controls that were not treated with prolactin [144].

An analytical study in rats also suggested that increased plasma prolactin can protect rat cardiomyocytes against intermittent hypoxia via phosphorylated Janus activator kinase (p-JAK2) and phosphorylated signal transducer activator of transcription factor 5 (p-STAT5) pathways for cell multiplication [143]. The same study also outlined that prolactin also protects cardiomyocytes by activating survival pathways such as PI3Kα/AKT and MAPK pathways through insulin-like growth factor 1 (IGF-1) [143].

Prolactin was also found to induce vasodilation in a study involving rat aortic rings [145]. This effect is mediated via increased NO production through the phosphorylation [145].

Pathophysiological effect of prolactin during pregnancy

Serum prolactin concentrations are associated with an adverse cardiovascular risk profile [146, 147]. A population-based study of (sample size 3929) men and women who were followed for 10 years observed a positive association of serum prolactin concentration and cardiovascular disease mortality [147]. Additionally, studies in the acute phase of coronary syndromes, ischemic strokes and transient ischemic attacks also reported elevated plasma prolactin [148]. The pathophysiology of prolactin is attributed to vasoinhibins rather than the full-length (23 kDa) prolactin [149–151].

Role of vasoinhibins in the pathophysiology of prolactin Vasoinhibins are smaller versions of prolactin resulting from proteolytic cleavage by cathepsin D or matrix metalloproteases [151]. All vasoinhibins contain the N-terminal region of prolactin and can interfere with angiogenesis by hindering endothelial cell migration, proliferation, differentiation and survival [151]. Vasoinhibins are sometimes known as the 16K-PRL.

Evidence showed that the 16K-PRL inhibits vascular endothelium growth factor (VEGF)-induced NO synthase (NOS) activity in endothelial cells which may mediate the antiangiogenic properties [152]. VEGF quickens endothelial cell proliferation via activation of the MAPK signalling cascade. Martine et al. [153] also proved the inhibition of the downstream kinases, Raf-1 and MAPK by 16K-PRL. Obstruction of eNOS activation can also lead to inhibition of vasodilation [152].

16K-PRL also induce cell apoptosis in vascular endothelial cells [153, 154]. The induced apoptosis is linked to rapid instigation of caspases 1 and 3 [154]. In bovine adrenal cortex capillary endothelial cells, Tabruyn et al. also noted the involvement of nuclear factor kappa B (NF-κB) in the activation of the caspase cascade by 16K-PRL [154].

In a study involving guinea pigs, 16K-PRL injected directly into a vein caused coronary and iliac artery constriction [155, 156]. Another study in rats' isolated arteries also confirmed the vasoconstriction action of prolactin [145]. However, evidence of vasoconstrictive action of prolactin in clinical studies is still controversial [157].

Recent data showed that 16K-PRL is implicated in the pathogenesis of PPCM (PPCM) [40]. Due to increased oxidative stress, the full-length 23-kDa prolactin is cleaved into the antiangiogenic, proinflammatory, and proapoptotic 16K-PRL [36]. The 16K-PRL will then directly impair endothelial function and trigger the release of micro-RNA 146a, which, in turn, has detrimental effects on cardiomyocytes [42]. The miR-146a internalised into cardiomyocytes will then suppress the neuregulin/ErbB pathway, thereby promoting cardiomyocyte apoptosis leading to heart failure [42, 158, 159].

Mechanisms of action of prolactin

The PRL activities are facilitated by the prolactin receptor (PRLR), which belongs to the cytokine receptor class 1 superfamily [157]. The classical PRLR is expressed in various tissues including the heart [157, 160]. There are three other isoforms of PRLR derived from proteolytic digestion of the full-length PRLR [157]. Abundant isoforms of PRLR

are: the full-length activating receptor-long form (LF), intermediate (IF) and short form (SF). However, a soluble isoform known as the PRLR-binding protein also exists [160].

JAK2-STAT cascade is the predominant pathway employed by PRL, although it can engage in other different second messenger cascades of signal transduction [157, 161]. Figure 4 summarises the mechanism of action of PRL. Ligand-mediated instigation of PRL-R causes tyrosine phosphorylation of numerous cellular proteins, including the receptor itself [157]. These activated isoforms bind to the STAT proteins which also become activated and form dimers which then migrate to the nucleus, where they regulate genes such as β-casein, β-lactoglobulin, interferon-regulatory factor-1 and others [157].

Interaction of the pregnancy hormones in the cardiovascular system

Hormones, apart from interacting with cells and cell receptors, also interact with each other. Hormone–hormone interaction could be synergistic, antagonistic or permissive. Both oestrogen and progesterone exert several effects of on the vascular function. They both stimulate vasodilation via promoting eNOS expression and NO-mediated relaxation [162–164]. Migliaccio et al. showed a physical interaction of the progesterone with the ER, which is an association necessary for progesterone to stimulate a signal transduction pathway, the MAPK pathway [165].

However, oestrogen and progesterone interaction, and cross talk could also be antagonistic [163]. In animal studies, medroxyprogesterone acetate counteracts the positive outcomes of oestrogens on endothelial function and coronary artery plaque size [166, 167]. Adams et al. demonstrated that the atherosclerosis extent of surgically postmenopausal cynomolgus monkeys, fed atherogenic diets and treated with hormones for 30 months, improved by 72% when treated with oral conjugated equine oestrogens (CEE) [166]. However, when treated with CEE plus medroxyprogesterone acetate (MPA) or MPA alone the atherosclerosis extent matched that of untreated controls [166].

In another study, progesterone hinders the ability of oestrogen to stimulate NO production in porcine arteries [155]. The same study also found that oestrogen can block progesterone-induced endothelial dysfunction and superoxide anion production [155]. This was again confirmed in ovariectomised mice where the vasoprotective effect of oestrogen on antioxidant enzyme expression and activity was prevented by co-injecting progesterone, resulting in added NADPH oxidase activity and reactive oxygen species (ROS) [167]. Surprisingly, clinical observational studies that evaluated treatment with oestrogen combined with progesterone in hormone replacement therapy (HRT) found comparable protective effects from combined oestrogen and progesterone

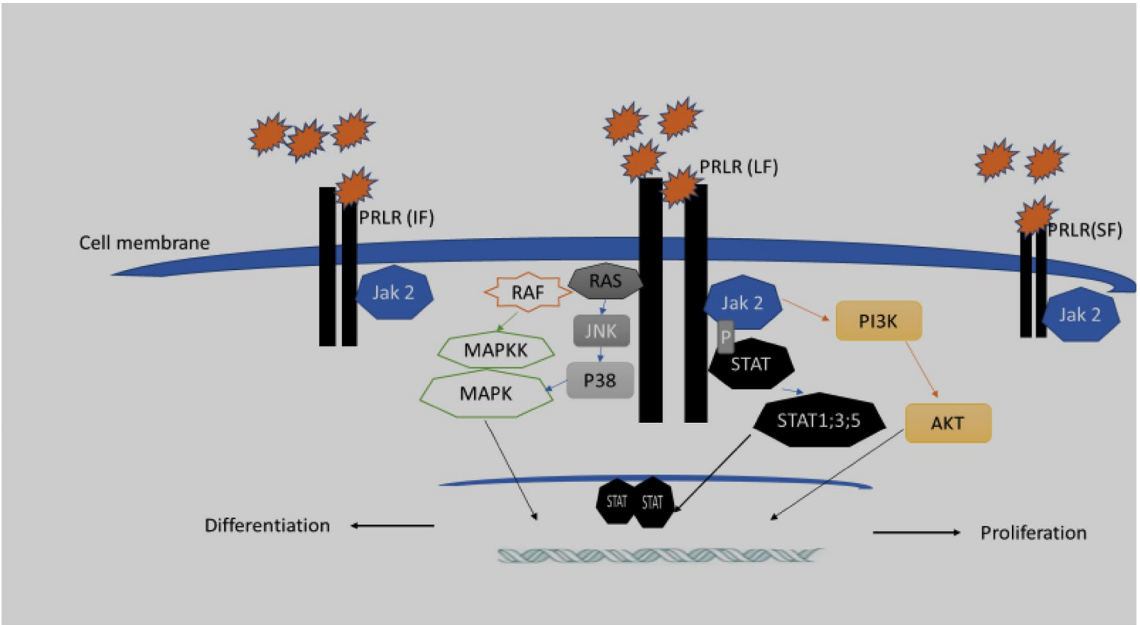

Fig. 4 Mechanism of prolactin action. The prolactin mechanism is facilitated by one of the three receptors; small, intermediate or full length. Prolactin involves several transduction pathways. However, the most dominant pathway is the Janus-activated kinase 2-signal transduction activation of transcription factor (Jak 2-Stat pathway). Other pathways such as the protein kinase (AKT) and mitogenic-activated protein kinase (MAPK) are also activated which, together with transcription factors, modulate several genes for cell differentiation and proliferation

just as that of oestrogen alone on the risk of coronary heart disease [168, 169].

The interaction of prolactin with other pregnancy hormones has not been thoroughly exploited. Interestingly, Malinari et al. found that treatment of porcine aortic endothelial cells with prolactin led to low levels of NO secretion and of the phosphorylation of ERK, Akt, and p38 [156]. Hence, prolactin may have antagonistic vasoconstrictive effects on both oestrogen and progesterone.

Conclusions

Hormones play an important role in maintaining physiological cardiovascular system during pregnancy. Hormonal concentration, availability of receptors and receptor concentration determine the extent of hormone impact. In addition to the individual effects of each hormone, hormones also interact with each other. It is crucial to study the interaction of hormones during pregnancy for a better understanding on cardiovascular diseases related to pregnancy. However, studies investigating the interaction of pregnancy hormones and its effects on the cardiovascular system are limited.

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