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Preeclampsia and Fetal Congenital Heart Defects

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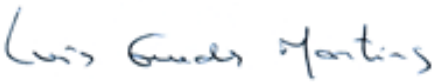

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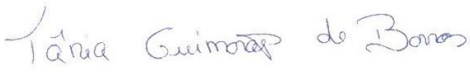

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Resumo

Uma placentação inadequada é referida como o mecanismo envolvido na fisiopatologia da pré-eclâmpsia. É sugerido que a disfunção endotelial, a implantação anómala e a insuficiência placentar podem explicar a associação entre pré-eclâmpsia e defeitos cardíacos congénitos fetais. O objetivo é então compreender se a pré-eclampsia materna aumenta o risco de desenvolvimento fetal de defeitos cardíacos congénitos. Ao pesquisar as múltiplas vias vasculogénicas, os fatores epigenéticos e ambientais, os desequilíbrios angiogénicos e a exposição a stress hipóxico patológico foram destacados e associados a um aumento do risco de doença cardiovascular, estando a maioria dos fenótipos de defeitos cardíacos ativamente associados a pré-eclâmpsia pré-termo. É também demonstrado que fetos com um diagnostico pré-natal de defeitos cardíacos congénitos apresentam um risco aumentado de várias comorbilidades incluindo restrição de crescimento intrauterino. O impacto da pré-eclâmpsia vai para além da gravidez, aumentando o risco de doenças futuras, quer nas mães quer na sua descendência. A importância da investigação desta associação entre pré-eclampsia e defeitos cardíacos congénitos fetais é demonstrada e reforça a necessidade de estudos futuros na prevenção e tratamento.

Palavras-chave: placenta, invasão trofoblástica, pré-eclâmpsia, defeitos cardíacos congénitos, hipertensão na gravidez

Abstract

An inadequate placentation is referred as the mechanism behind the development of PE. It is suggested that endothelial dysfunction, impaired implantation and placental insufficiency may explain the association between PE and fetal CHD. The aim is to understand whether women with PE increase the risk of fetal CHD. By researching the multiple vasculogenic pathways associated to heart defects and PE, epigenetic and environmental factors, angiogenic imbalance and exposition to pathological hypoxic stress were enhanced, increasing the risk of CVD, being most of the heart defect phenotypes actively associated to preterm PE. It is also shown that fetuses with a prenatal diagnosis of CHD have an increased risk of several comorbidities including IUGR. The impact of PE goes beyond pregnancy increasing the risk of diseases later in life in both offspring and mothers. The importance of investigating this relationship between PE and CHD is demonstrated and reinforce the requirement of future research in prevention and treatment.

Keywords: placenta, trophoblastic invasion, preeclampsia, congenital heart defects, pregnancy hypertension

Abbreviations

Aa	Late diastolic waves
AI	Augmentation index
aIMT	Aortic intima-media thickness
ANS	Autonomic neural system
AT1 AA	Angiotensin II type I receptor antibodies
BMI	Body mass index
BNP	Brain-type natriuretic peptide
Ca^{2+}	Calcium
CCO	Combined Cardiac Output
CHD	Congenital Heart Defects
CRP	C-reactive protein
CVD	Cardiovascular disease
CKD	Chronic kidney disease
DMP	Differentially methylated positions
DNAm	DNA methylation
Ea	Early diastolic waves
ESRD	End-stage renal disease
FPU	Feto-placental unit
GO	Gene ontology
GMD	Gestational diabetes
HIF	Hypoxia-inducible transcription factor
HLHS	Hipoplastic Left Heart Syndrome
HR	Heart rate
HRV	Heart rate variability
IFI	Isthmus blood flow index
IUGR	Intrauterine Growth Restriction
MATcKO	Maternal conditional knock-out of HIF1α
MCA	Middle Cerebral Artery
MPI	Myocardial Performance Index
O_2	Oxygen
ODD-Luc	Oxygen degradation domain HIF-1α fused to luciferase
PE	Preeclampsia
PI	Pulsatility Indices
PHD	Prolyl hydroxylase domain
PlGF	Placental growth factor
PWV	Pulse wave velocity
ROS	Reactive oxygen species
sEng	Soluble endoglobin
sFlt-1	Soluble form of fms-like tyrosine kinase-1
SLE	Systemic lupus erythematosus
SV	Single Ventricle (non-HLHS)
TB	Throphoblast
UA	Umbilical Artery
uNK	Uterine Natural Killer
VEGF	Vascular endothelial growth factor

Index

Introduction

Congenital heart defects (CHD) correspond to the largest group of congenital malformations[1], affecting about 1% of live births. CHD is the leading birth defect and cause of infant morbidity and mortality with the higher hospitalization costs[2]. Preeclampsia (PE), an entity that presents two stages, one representing fetoplacental processes and another one the maternal symptoms in response to the first stage, is seen as possibly related to the development of CHD[1]. Initially, the suggestion was that an impaired placental development in PE could explain the link between PE and fetal CHD, yet it wouldn't explain the predisposition in subsequent pregnancies[3]. It is thought that endothelial dysfunction, poor implantation and placental insufficiency are involved in the etiology of early-onset PE[4]. As well, maternal signalling and immunity are the two factors involved in implantation, so placental insufficiency and concomitant CHD may result from disruption in maternal signalling and an excessive maternal immunity[2]. Though lots of researches are around genetic etiology, it can derive from undiscovered functions of noncoding genetic, epigenetic and environmental factors, common to both PE and CHD, what makes the implication of placental abnormalities in CHD easier to understand, regardless of being causal, commensurate or reactive[2]. Increasing evidence suggests that during early pregnancy, hypoxia can lead to an inadequate trophoblastic invasion, and consequently to placental insufficiency and abnormal development of the fetal heart[5]. Additionally, hypoxia plays as an important modulator of normal fetal and placental vasculature expansion, whose defects can lead to CHDs and to a progressive fetal vulnerability secondary to O_2 deprivation[6].

Studies carried out over the years revealed that pregnancies complicated by preterm PE are associated with a more than three times higher prevalence of major CHD and the same prevalence is seen the other way around[7]. Besides this, the association between late-onset PE and severe CDH was seen for severe PE[1]. Women with previous pregnancies with CHD had a 2 times greater risk of early PE, while a previous pregnancy with early PE had a 6 times greater risk of CHD in the present pregnancy[3].

Disturbances of angiogenic factors early in pregnancy are considered the connection between maternal PE and fetal CHD[1], not only in the same pregnancy but also across pregnancies, which is demonstrated by an increased risk of CHD in a current pregnancy associated with an early and late preterm PE in a previous one[4].

The possibility of initiating the study of the placenta earlier in pregnancy using more advanced technologies is fundamental to see if the identified placental disturbances are evident within the maternal circulation and across the extent of CHDs[2]. Why the risk of severe CDH increases when

associated with early-onset PE compared to its other subtypes, what it is expected for woman with this association in previous pregnancies in the future ones, are questions still to be clarified[1].

Methods

To compose this review, thorough literature searches were repeatedly conducted in PubMed and Medline with a limitation of articles written in the English language. The search terms used were placenta, trophoblastic invasion, preeclampsia, congenital heart defects, and hypertension. The keywords were searched individually and jointly.

Clinical trials, meta-analyzes, clinical studies and systematic reviews from the last 20 years were selected. It was established a time limit for searching publications until March 31, 2020.

Initially, all the articles were selected based on the title e subsequently on the abstract. From the remaining manuscripts, the selection was based on the complete reading of the articles, according to the content, relevance and medical journal. Additionally, the references of all analysed studies were searched to obtain necessary information.

The inclusion criteria englobe original articles, integral article available and the search was established in three notions including pregnant women and their offspring as study populations, the exposition to pregnancy adversities, in particular PE and the development of cardiovascular disease as its outcome. Duplicate articles and all studies that did not address CHD or its relationship with PE were excluded.

Lack of oxygen in fetal and placental development and congenital heart defects

During the normal embryonic development hypoxia is expected, and its signalling through hypoxia-inducible transcription factor (HIF) is essential for the development of fetal and placental vasculature[6]. An increase in oxygen (O_2) supply as a result from the functional maturation of the feto-placental unit (FPU) occurs in the end of the 1st trimester[8] (Figure 1).

Prolyl hydroxylase domain (PHD) enzymes and their substrates, HIFs, are considered the best O_2 sensing system. Under hypoxia, HIF-1α accumulates due to the decreased activity of PHD and activate the hypoxia-inducible gene program that promotes an increase in red blood cell production and O_2 transport[6]. Using oxygen degradation domain HIF-1α fused to luciferase (ODD-Luc), an indicator of tissue oxygenation, whose activity varies with the inhaled O_2 concentration, there was an increased susceptibility to O_2 deprivation at E11.5 due to FPU's immaturity[8].

Placental defects and deficits in oxygen delivery to the fetal organs submitted to hypoxic stress is caused by an inactivation of maternal HIF-1α at mid-pregnancy. Studies refer that besides endovascular trophoblast (TB) invasion and uterine vascular remodelling being activated by hypoxia, maternal decidua is invaded by maternally-derived uterine Natural Killer (uNK) cells, responsible for the regulation of trophoblast behaviours in a hypoxia-sensitive way[8].

A link between hypoxia and TB-cell dependent remodelling of the spiral arteries and PE/placental insufficiency is suggested by a superficial invasion of the decidua by fetal-derived TB cells in placentas from patients with PE[6].

Mouse models allowed the report that gene knock-outs can cause fetal CHD and placental defects. It is proposed that the recruitment of maternal-derivated uNK and fetal-derived TB cells requires hypoxia/ HIF-1α in the maternal compartment, in order to increase both placental blood flow and transport of O_2 to the fetal tissues. About the effect of MATcKO HIF-1α placental defects on placental function, the resultant placental insufficiency prolongs the phase of vulnerability for O_2 deprivation, increasing the risk of CHDs because it occurs during heart morphogenesis[6].

Both maternal PE and fetal growth restriction development occurs due to an unsettled angiogenesis in the placenta[9]. Vascular endothelial growth factor (VEGF) receptors may be involved in heart valve formation because defects in cardiac valve development were associated with their blocking[10]. Placental growth factor (PlGF) is a glycoprotein that promotes proliferation and activation of endothelial cells[10]. In pregnancies with isolated fetal heart defects there is evidence of lower PlGF suggesting that these fetuses may have intrinsically altered angiogenesis, present in both placenta and the fetal heart[10].

Comparing foetuses with and without CHD, as a result of chronic hypoxia, an increased VEGF-A

and soluble form of fms-like tyrosine kinase-1 (sFlt-1) expression and underproduction of PIGF was shown, suggesting that a placental anti-angiogenic environment combined with a heart-specific vascular defect can be the cause of CHD[10].

Summarily, CHD can derivate from impairment of common vasculogenic pathways of placental and fetal cardiovascular development due to an angiogenic imbalance; from a hypersensitive cardiac structure to pathological hypoxic stress, that occurs during placental formation; and from the extension of the exposure of the developing fetal heart to O_2 deprivation at midgestation, when organogenesis is occurring[6].

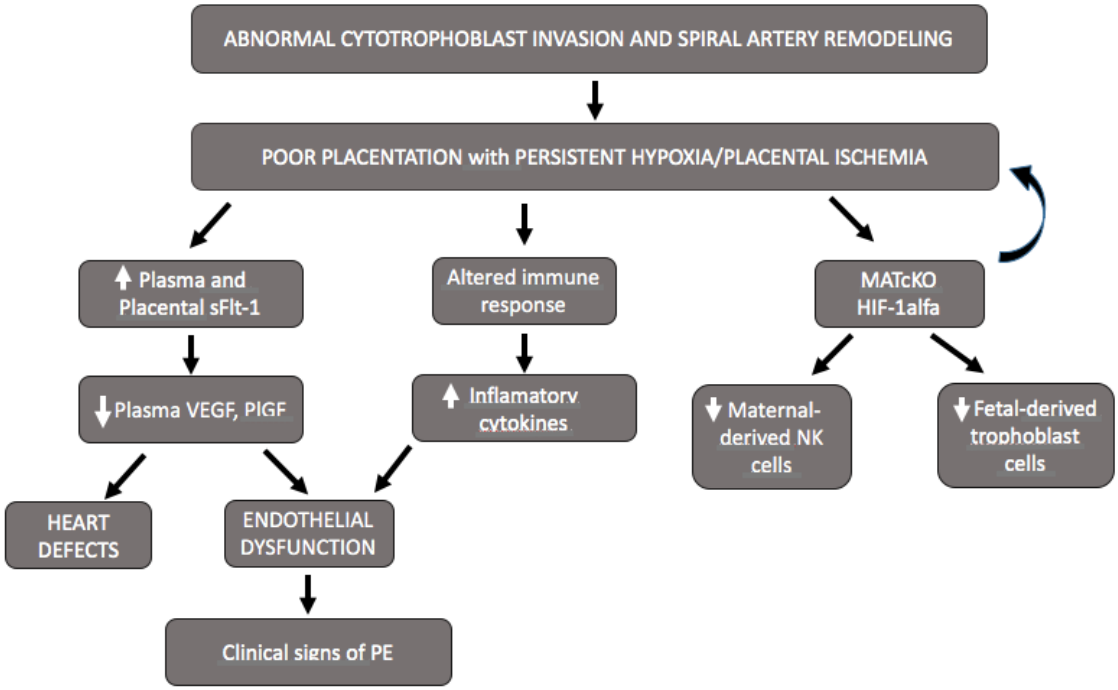

Figure 1. Schematic representation of the role of oxygen and lack of oxygen in feto-placental coupling. Abbreviations: HIF, hypoxia-inducible (transcription) factor; MATcKO, Maternal conditional knock-out of HIF1α; PlFG, placental growth factor; PE, preeclampsia; sFlt1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor.

Association between fetal Congenital Heart Defects and maternal risk for placenta-related complications

Pregnant women with CHD have significantly more placenta abnormalities like growth disturbances, PE, preterm birth and stillbirth[2], that suggests a relationship between impaired placentation and CHD[11].

The suggestion that an abnormal development of the fetus' heart can result from an intrinsic

abnormal angiogenesis[4] can be explained by the altered angiogenic pattern in maternal blood of pregnancies with CHD[12], with a higher resistance in uteroplacental blood flow[11]. As a response to an altered blood flow, the embryonic cardiovascular system alters its contractile function, promoting an abnormal tissue composition remodeling and subsequently CHD[13].

This relationship between an impaired angiogenesis and an inadequate heart development is supported by a decreased maternal serum PIGF, increased fetal anti-angiogenic levels and increased maternal sFlt-1 levels[11]. These alterations in the mothers' plasma concentrations increases the risk of delivery of a neonate with IUGR and/or development of PE[4].

Lots of studies, in both human and mouse, allowed to understand the role of genes involved in heart development of the fetus and its relation to abnormalities in the placental vascular tree[14], demonstrating that both, as vascular organs, share development concurrent pathways[2]. The regulation of cardiomyocyte specification and extra villous trophoblast invasion by Notch and Wnt, the formation of heart valves and septa and placenta that request identical genes like VegF and Connexin 43, being the last one essential in both intercellular placental communication and cell-cell interactions in cardiomyocytes are examples. Others studies include both disturbance of vascular cell adhesion molecule 1 (VCAM1) and deletion of the upstream gene FOXO1 resulting in an impaired placentation; the loss of peroxisome proliferator-activated receptor (PPAR gamma) leading to an unsettled placental and cardiac development resulting in embryonic lethality mid-gestation; and the knockout of Cited2 that is associated with a disorganized placental vasculature causing important heart and fetal growth defects[2].

After the development of both maternal-placental and fetal-placental circulations, the direct or indirect influence that the maternal environment can have in the placenta and heart growth, via the maternal circulation, needs to be considered[2]. Placental insufficiency and concomitant heart defects may result from disruptions in maternal signaling[15] and an excessive maternal immunity[14]. Using models with induced placental insufficiency, it was concluded a reduction in placental area contributed to depression of cell cycle activity and proliferation leading to an abnormal maturation and proliferation of fetal cardiomyocytes[16].

Certain maternal characteristics are associated with an increased risk of congenital malformations, such as maternal smoking[17], pre-existing diabetes and/or hypertension, obesity[18], gestational diabetes[19], and an unfavourable maternal lipid profile[20].

It is concluded that an altered endothelial development in the placenta increases the risk of heart disease, leading to an abnormal maturation and proliferation of fetal cardiomyocytes. So, the fetal cardiovascular development is influenced by alterations in maternal-fetal nutrition, cardiac load and placental function[16].

Fetal congenital heart disease and intrauterine growth restriction

Birth weight is an important factor associated with fetal CHD and its outcomes[21]. Lots of studies show an increased risk of IUGR in fetuses with a prenatal diagnosis of CHD, either isolated or in major forms. The physiopathology behind this association still to be clarified: if one is the cause of the other, or both have common causes[22]. The hypothesis that the coexistence of CHD and IUGR may be independent of each other, but common risk factors such as maternal periconceptional smoking, increased total maternal homocysteine levels or inadequate fetal hemodynamics are shared exists[23]. The temporal pattern between the diagnosis of both, makes CHD less likely to be caused by IUGR. But cardiac function may have a causal connection to fetal weight, because an inadequate ventricular function in fetuses with cardiovascular malformations lead to a decreased cardiac output and subsequently to a decreased perfusion, compromising the fetal growth[22]. Some authors suggest that ventricular ejection force is inversely related to severity of growth restriction[22].

In the evaluation of the distribution of circulation in patients with CHD, combined cardiac output (CCO), middle cerebral artery (MCA) and umbilical artery (UA) pulsatility indices (PIs) have been used in order to study their influence on fetal growth[21].

At birth, fetuses with CHD showed decreased values of femur length, body weight, length and chest circumference, and altered blood flow more frequently. Thus, the association between CHD and IUGR can be explained by the increased risk of an inadequate development, an impediment to fetal growth due to the presence of CHD[24].

Comparing smaller fetuses with CHD and normal hearts, while the second ones have the capacity to guarantee an adequate oxygen supply[21], in the first ones the association between IUGR and cardiac disturbances in its structure, function and electrophysiology has been made. "Cardiomyopathy–like" changes such as relative interventricular septum hypertrophy or increased left ventricular myocardial performance index (MPI) with no improvement in post-natal days, have been related to IUGR. This occurs as an adaptation to an increased myocardial workload in utero[25].

In severe CHD such as single ventricle (SV) anomalies, in response to cerebral hypoxia, the existent cardiac function isn't sufficient to increase the cerebrovascular flow leading to inadequate flow patterns, with oxygenated and deoxygenated blood being mixed intracardiacally[24]. This can lead to a symmetrical growth restriction, but SV foetuses have the ability to adapt to the inadequate deoxygenated blood due to the autoregulatory response of cerebral vasodilation[26].

On the other side, lower cerebrovascular resistance is associated with ischemic brain lesions in fetuses with IUGR. The placental failure with systemic oxygen desaturation is the principal cause of IUGR[26]. In order to compensate the hypoxia in placental insufficiency, an increase in blood flow to vital organs is done (brain, heart and adrenals), favouring their growth. Conversely, the blood flow to peripheral and placental circulations is decreased, preventing a symmetrical and adequate fetal growth. So, due to this preferable redistribution to the brain, Doppler measurement of a decreased MCA IP and an increased UA IP is demonstrated[24].

To mention that one of the most common causes of IUGR are chromosomal abnormalities, that have decreased due to improved 1st trimester screening[27]. Miller-Dieker lissencephaly syndrome[28] and Johanson-Blizzard syndrome[29], are examples, with CHD and IUGR as their main features. Also, Turner's syndrome, characterized by a monosomy of the terminal segment of the short arm of the X chromosome that encodes the SHOX gene, associated to growth disturbances starting before birth leading children to have short stature, that can occur due to IUGR[30].

In conclusion, the likelihood of CHD infants of having IUGR is higher, what matters in terms of their fetal surveillance, treatment and prognosis[23].

Preeclampsia and fetal heart structure and function

PE, as a primary cardiovascular disorder can be demonstrated by the findings around common underlying factors and genetic loci shared between them.[3,31]. The remained question is how it compromises the development of a normal fetal heart[32].

The time during when the embryonic development of the heart occurs is expected to be the same in which the severe CHD, assumed as errors in cardiac development, tend to develop[1]. In embryonic heart, initially represented by a primitive tube, the beating initiates before the conduction system and a valvular mechanism are developed[33]. As the embryonic body develops, both the cardiac output and heart rate (HR) increase in a proportionally way[33]. Until the end of the 1st trimester, the diameter of the outflow also increases, during the increased umbilical resistance, what means that a substantial increase in the umbilico-placental volume of blood flow must occur. So, it adapts to the hypoxemic intrauterine environment in order to develop adequately in a structural, physiological and functional way, and becomes essential when the passive oxygen diffusion isn't enough to the embryo in development[34]. Finally, the cardiac organogenesis completes and the diphasic diastolic filling of the atria starts, what is representative of an umbilico-placental circulation that is more active[33].

In preeclamptic pregnancies, there is the association between utero-placental insufficient perfusion and an increase in the umbilical resistance, in which the smooth muscle cells near the placental arteries differentiate and proliferate, ultimately affecting the development of the heart[33]. So, an altered fetal cardiac function can derivate from an increased fetal cardiac afterload resulting of an increased placental vascular resistance[35]. Not only fetal cardiac afterload but also preload can be impaired in PE leading to alterations in systolic and diastolic function[32]. The systolic dysfunction associated to an increased isovolumetric contraction time was considered its major component. This means that in PE so that there is an inadequate pressure to open the aortic valve, a greater myocardial contraction is required[36]. The global diastolic dysfunction and the incapacity to adapt to increased load of volume and pressure[37], can lead to left ventricular dysfunction and arterial stiffness respectively in PE[36, 38].

Even adolescents born from preeclamptic mothers showed structural abnormalities[39] such as increased myocardial wall thickness and concentric remodelling associated to decreased end-diastolic volume[40].

Also, to notice that the vascular dysfunction conditioned by PE can include the production of reactive oxygen species (ROS) and an abnormality in intracellular Ca2+ signalling, meaning that the "programming" of the fetal cardiovascular system can be affected by the inadequate redox state in PE, leading to a dysfunctional Ca2+ signalling in fetal umbilical endothelial cells[41]. Thus, cardiac dysfunction and alterations in both morphogenesis and ventricular function are shown when exposed to hypoxia. It was established that before week 10 of gestation, the fetal organogenesis is not unsettled due to the insensibility of cytotrophoblast cells to hypoxia but after, the risk is considerably higher[42]. So, the adaptation of the fetal cardiovascular system in order to promote a preferential oxygenation of the heart and brain by the placenta is essential[34].

In order to evaluate how the HR behaves and to understand the abnormalities in its regulation, the estimation of the local smoothness of the FHR can be useful[43, 44]. In fetuses of preeclamptic pregnancies, during gross fetal movement, when the magnitude of the FHR variation is expected to be larger, it showed to be abnormal[43, 44]. Being the parasympathetic nervous system the modulator of the regulation of the local smoothness, these alterations occur due to a dysfunctional autonomic nervous control of FHR, what may invalidate the setting of a healthy ontogeny[43, 44]. So, the Autonomic Neural System (ANS) dysfunction can be included in the pathogenesis of PE and fetuses affected by severe PE can have their heart rates affected in terms of instability and frequency-domain variability. Also, with the increased severity of PE, the mean sympathovagal balance was shown to be increased[45]. While in preeclamptic women, the heart rate variability (HRV) is modulated by the sympathetic hyperactivity, in their offspring the autonomic dysfunction results in fetal distress with supressed fetal biophysical activity. So, the

association between autonomic control and endothelial function can be made in PE increasing the risk of cardiovascular complications[45].

Through echocardiographic and biochemical measurements, cardiac abnormalities in both structure and function were demonstrated in PE, such as heart enlargement and hypertrophy, and increased MPI[39], a tool used to report global myocardial function[36] respectively. Using a Doppler echocardiography, the evaluation of cardiac functions included the mean peak values of three early diastolic waves (Ea) and of three late diastolic or atrial filling waves (Aa), and it was demonstrated that both Ea and Aa, and its ratio (Ee/Aa) were significantly lower when measured in the interventricular septum, the left ventricle lateral wall and the right ventricle free wall[32]. Other predictors of deterioration of cardiac function include aortic isthmus blood flow index (IFI)[46], decreased aortic and pulmonary peak systolic velocities (PSVs), faster HR per minute and prolonged deceleration time of early mitral inflow[32]. Also, it is proposed that the neonates risk of CHD begins in utero when exposed to PE and is associated to increased cardiac troponin T[47] and troponin I levels[39]. Another predictor of heart damage is BNP, especially NT-proBNP, as it is a marker of early cardiac damage released in response to ventricular stress with a higher sensibility[47].

As conclusion, lots of studies showed that most heart defect phenotypes were strongly associated with preterm PE[4].

Preeclampsia as modulator of offspring health

Lots of studies demonstrated that during the critical time when organ development is occurring, the exposition to adverse environment in utero can result in increased risk of diseases later in life[48, 49]. PE is one of the many pregnancy disorders that influences the intrauterine environment through different triggers[50, 51], what happens reciprocally, by promoting maternal and offspring vascular system alterations, resulting in systemic homeostasis and disturbances in the development and function of blood vessels[50] (Figure 2).

These triggers that can act as initiators and mediators of cardiovascular and metabolic diseases include angiogenic disparity, angiotensin II type I receptor antibodies (AT1 AA) and inflammatory milieu[51]. These mechanisms lead to the release of circulating factors such as sFlt and sEng that are involved in the programming of progeny cardiovascular disease (CVD), ultimately increasing the vulnerability to CVD later in life[48]. Also, when exposed to hypoxia, there is an inadequate placental function and consequently the development of inflammation and atherosclerosis, programming the offspring blood pressure[48].

It is established that the ROS act as mediators, and the cellular adaptations (nephrons, beta cells and cardiomyocytes) and epigenetic alterations as effectors[51], and they can all be involved in the development of chronic diseases later in life[52] including hypertension[53, 54], type 2 diabetes, obesity, atherosclerosis[55] or metabolic syndrome[51].

These alterations in gene expression, maintaining the underlying DNA sequence, referred as epigenetics, can be useful in the diagnosis and prognosis as biomarkers of unfavourable outcomes, including altered DNA methylation (DNAm)[48], and renin-angiotensin-aldosterone mRNA upregulation[49] DNAm experience alterations throughout different stages of life[56, 57], so the possibility that these alterations can be responsible for the risk of transmission to future generations is considered[48, 57]. The suggestion that lots of identified gene-ontology (GO) related to differentially methylated positions (DMP) genes can influence the CV programming of offspring exposed to PE associated to altered DNA methylation was made[54].

Prenatally hemodynamics can be associated to alterations in cardiac structure and function later in life, what is suggested by offspring exposed to maternal PE presenting low cardiac mass what can be related to high resistance in the umbilical artery[58] and other cardiac disorders such as global diastolic dysfunction, increased resistance circulatory slow output, low cardiac output and decreased cardiac reserve[52]. They also display left ventricle remodelling in the postpartum period that tend to aggravate with age and emergence of CVD risk factors, with greater relative wall thickness[58], being the left ventricle dysfunction and hypertrophy predominant in preterm PE[52]. So, it is suggested the association between the exposition of children in utero to PE and the increased risk of CVD with increased rates of arrhythmias, heart failure[59], coronary and peripheral arterial diseases[60]. There was also an increased risk of pulmonary artery pressure in offspring exposed to maternal mild and moderate PE[53]. So, in both pulmonary and peripheral vascular systems the vascular stiffness was increased[51].

Offspring from preeclamptic pregnancies have also an increased risk of stroke[58] that can have the contribute of an inadequate brain blood perfusion and decreased left ventricular end-diastolic volume[50, 51]. While in severe PE the risk of thrombotic stroke was elevated, in offspring of mild to moderate PE the hemorrhagic one was predominant[53].

Neonates exposed to PE in utero by presenting increased aortic intima-media thickness (aIMT) and cord blood triglyceride, and decreased cord blood high density lipoprotein and cholesterol levels, demonstrated that a possible atherogenic phenotype may be behind the association they established with later life CVD[48]. They also presented a higher body mass index (BMI) [48, 58] and increased plasma glucose[61], factors that are shared with the metabolic syndrome, what enhance one more time the risk of CV and metabolic diseases[51].

When it comes to the renal system, pre-term and low birthweight offspring, two conditions that

usually co-occur with PE, tend to present a decreased number of nephrons what leads to a decreased rate of renal ultrafiltration and ultimately to an increased blood pressure. The risk of hypertension is increased due to the association between glomerular hypertrophy and decreased renal vascular dilation[48].

They also have an increased risk of neurodevelopment, psychiatric, endocrine[48, 50, 52, 62] and immune disorders[53], with an increased risk of hospitalizations in the earlier years[51, 60].

It was shown that women or men born from preeclamptic pregnancies have a higher risk of developing a pregnancy complicated by PE[48]. When it comes to the mortality risk, it was increased from CVD in offspring exposed to hypertensive diseases in utero[58, 60].

Due to the long-term significance of PE on the CV health of the offspring[60] preventive strategies targeting primary CVD may be essential[48, 63].

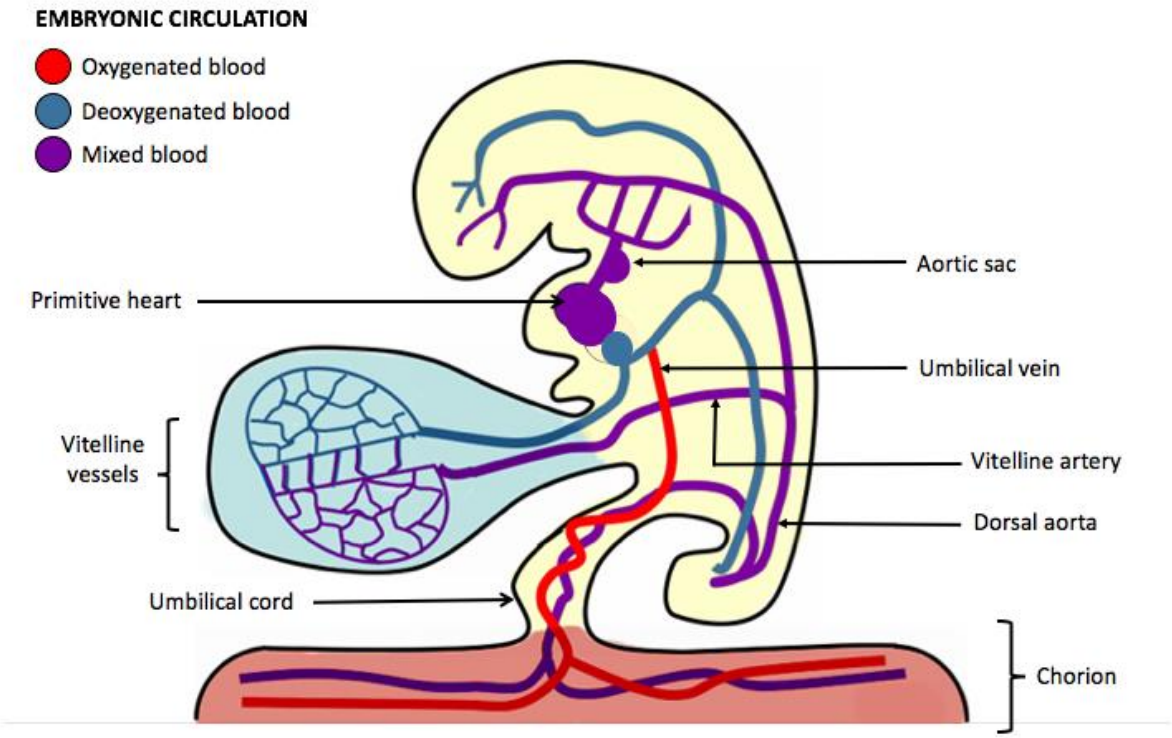

Figure 2. The embryonic cardiovascular system (21 days). The embryonic vasculature allows the connection between the placenta and heart. During organogenesis, maternal-embryo transport can be influenced by vitelline vascular system, before the establishment of the of the chorionic circulation at the end of the 1st trimester. Alterations in the resistance of placental, embryo and vitelline circulations may affect the differentiation of the embryo/fetal cardiomyocytes ultimately leading to both placenta and heart structural disturbances.

Preeclampsia as a predictor of maternal cardiovascular disease

PE is considered one of the major causes of maternal mortality and it is known that is not restricted to pregnancy[62, 64], being the risk of CV events increased later in life[59, 65].

It is associated to increased endothelial dysfunction[66, 67] and total vascular resistance that by augmenting afterload leads to alterations in cardiac function. This cardiac dysfunction may be associated to higher levels of sFlt-1[68] and sEng[69] that may promote coronary vasoconstriction and eventually lead to the development of myocardial ischaemia, cardiac fibrosis[68] and peripartum cardiomyopathy[70]. So, sFlt-1 levels instead of decreasing after delivery of the placenta, are maintained by a continual anti-angiogenic milieu, what increases the risk of CV disease[71].

As a consequence of inadequate placentation, these women may present an altered cardiometabolic profile[72, 73]. It is proposed that the association of PE and CVD can come from risk factors shared between them[50, 74, 75] including smoking, increased BMI and LDL cholesterol, diabetes mellitus or family history of coronary heart disease[76, 77], or from the proatherogenic status of pregnancy[78], in which the atherosclerotic lesion in the utero-placental spiral artery isn't sorted out after the birth[77, 79].

In women with a previous exposure of PE the blood pressure regulation is associated to increased sympathetic activity[80], what leads to decreased baroreflex sensitivity and changes in extracellular volume. So, this increased sympathetic activity may result in an increased CV morbidity and mortality with several systems being affected[68].

It is acknowledged that women with PE are subjected to an increased CV risk[59, 72], including other vascular diseases such as hypertension, diabetes, thromboembolic or cerebral events[48, 81, 82], and eventually end-stage renal disorder[62, 83] and premature death[84]. They have an increased risk of elevated systolic and diastolic blood pressure in the first years after delivery, that can progress to hypertension later[68], what compared to women with normotensive pregnancy tend to develop years earlier with a decreased life expectancy[85]. Also the prevalence of an increased BMI in women previously exposed to PE during pregnancy showed to be increased, what by itself may influence blood pressure[86].

After delivery and at long term, alterations such as diastolic dysfunction[87], inadequate contractility[71], LV hypertrophy[79, 88] with increased left-atrial end-diastolic volume and increased relative wall thickness suggestive of structural remodelling and inadequate response to volume expansion were present in former preeclamptic mothers[89]. Also, increased carotid intima-medial thickness[90], high blood pressure[50], increased coronary artery calcification[91] and dyslipidaemia[61] were shown.

There are vascular indexes that can help anticipating the maternal outcome, such as higher augmentation index (AI) and pulse wave velocity (PWV) used to estimate arterial stiffness. Maternal age during the development of PE influences the degree of endothelial impairment, which is more noticeable in younger women[50].

The risk of maternal CV disease later in life is also potentiated by preterm delivery, depending on the cause of prematurity, which is also associated to an increased risk of angina pectoris[52], coronary heart disease, stroke, heart failure[74], arrhythmias and necessity of CV hospitalizations[92, 93]. They also tend to present echocardiographic alterations[52, 71]. This association can be partially explained by metabolic alterations including weight gain and type 2 diabetes mellitus, but vascular disorders, especially PE are an essential part in it, with an even greater risk if it is recurrent[92, 94, 95]. So, the risk of early cardiac, cerebrovascular and peripheral vascular disease is increased in women with previous PE[67].

The risk of end-stage renal disease (ESRD) [83] and chronic kidney disease (CKD) [96] is also increased. These women may present alterations in albuminuria and eGFR that later in life may eventually contribute to increase the risk of CV and renal diseases[68, 83], with an increased risk of mortality deriving out of renal disease[97].

In women with an atherogenic lipid profile[98] the risk of CVD was increased, in which higher levels of triglycerides and cholesterol are definitely associated to PE and increased blood pressure years after delivery[74], contributing to metabolic and inflammatory routes[99], with increased levels of c-reactive protein (CRP) [100].

It is established a higher risk of CVD later in life in women with a history of PE, that increases with each pre-eclamptic pregnancy[59], in more severe forms[76] and generally with an also higher risk of happening sooner in life[101]. There is an increased risk in African-American women[102] and in women with systemic lupus erythematosus (SLE) what is expected by renal disease and systemic inflammation[66, 103].

Being the association of genetic predisposition and negative lifestyle recognised as predictor of higher susceptibility[104], the alteration of behaviour and lifestyles may help reducing the risk of CVD[74].

Discussion and future research

The development of PE may have as its main mechanism an inadequate placentation[105], whose pathogenesis include increased resistance in maternal uterine circulation, altered placental perfusion and exposition to antiangiogenic stress as its components[3]. Then, the predominance of

apoptosis, hypoxia and oxidative stress[6, 105] can eventually lead to an altered trophoblastic invasion precipitating the emergence of placental insufficiency and the development of fetal CHD[5], that are considered the largest group of congenital malformations[1] and the leading birth defect[2].

The association of an intrinsic inadequate angiogenesis and abnormal development of the fetus' heart[4] is suggested by alterations in its contractile function, altered remodelling and ultimately CHD[13] in response to higher resistance in uteroplacental blood flow[11]. Disruptions in maternal signalling[15] and an excessive maternal immunity[2] showed to also be responsible for placental insufficiency and concomitant CHD[14].

To notice that endothelial dysfunction in the placenta decreases the placental area what by being associated to alterations in the differentiation and proliferation of the smooth muscle cells near the placental arteries[33], eventually leads to disorders in the maturation and proliferation of fetal cardiomyocytes, increasing the risk of CVD[16].

The "programming" of the fetal cardiovascular system is conditioned by the production of ROS and alterations in intracellular Ca2+ signalling in fetal umbilical endothelial cells, presented in PE[41], what means that the exposition to hypoxia leads to the emergence of cardiac dysfunction and alterations in cardiac morphogenesis[42.]

The increased prevalence of placenta abnormalities like growth disturbances, PE, preterm birth and stillbirth[2] in women whose fetuses have CHD, supports the association between impaired placentation and CHD[11]. In fetuses with a prenatal diagnosis of CHD, the risk of IUGR is increased[21], just like the presentation of decreased femur length, body weight, length and chest circumference values at birth[24]. A causal connection between them can be explained by fetal growth being compromised by decreased perfusion as a response to ventricular dysfunction and decreased cardiac output[22]. So, the placental failure with systemic oxygen desaturation is the principal cause of IUGR[26], restricting a symmetrical and adequate fetal growth due to the decreased blood flow to peripheral and placental circulations[24]. In addition, this association is sustained by decreased maternal serum PIGF, increased fetal anti-angiogenic and maternal sFlt-1 levels[10, 11], that promotes the risk of maternal PE and delivery of a neonate with IUGR[4].

In PE, the increased placental vascular resistance can lead to increased fetal cardiac afterload[35] and preload, resulting in an altered systolic and diastolic cardiac function[32] that along with the maladaptation to increased load of volume and pressure[37] promotes the left ventricular dysfunction and arterial stiffness[38]. Alterations in the fetuses' heart rates in terms of instability and frequency-domain may be promoted by the ANS dysfunction, another component of the pathogenesis of PE that increases the risk of cardiovascular complications[39]. Biochemically, increased cardiac troponin T[47], troponin I[39] and NT-proBNP levels showed to be present[47].

As offspring of preeclamptic pregnancies, the exposition to adverse environment in utero during organogenesis can result in increased risk of diseases later in life[48, 49]. Angiogenic disparity, AT1 AA and inflammatory milieu promote the releasing of circulating factors such as sFlt and sEng[51], that are involved in the programming of progeny CVD[48]. While the ROS and act as mediators, the cellular adaptations and epigenetic alterations act as effectors of the development of chronic diseases later in life[52] including hypertension[53, 54], type 2 diabetes, obesity, atherosclerosis[55] or metabolic syndrome[51].

The development of cardiac abnormalities[39] such as increased myocardial wall thickness and concentric remodelling associated to decreased end-diastolic volume[40], global diastolic dysfunction, low cardiac output and decreased cardiac reserve[52], increases the rates of arrhythmias, heart failure[59], coronary and peripheral arterial diseases[60] later in life. They have also an increased risk of stroke[58], increased BMI[48], plasma glucose[61], aIMT and cord blood triglyceride, and decreased cord blood HDL and cholesterol levels, which highlights the possibility of an atherogenic phenotype behind an increased risk of CVD[48]. The risk of offspring born from preeclamptic pregnancies of developing a pregnancy complicated by PE is also increased[48], just like the mortality risk[58].

Former preeclamptic mothers showed to be exposed to the outcomes of PE that are not limited to pregnancy and are one of the main causes of maternal mortality[62], with an increased risk of CV disorders during pregnancy and later in life[59], such as myocardial ischaemia, cardiac fibrosis[68] and peripartum cardiomyopathy[70], and hypertension, diabetes, thromboembolic or cerebral events[48], and eventually end-stage renal disorder[83] and premature death[84] respectively.

Former preeclamptic mothers showed disorders indicative of structural remodelling and inadequate response to volume expansion including diastolic dysfunction[87], inadequate contractility[71], LV hypertrophy[79, 88] with increased left-atrial end-diastolic volume and increased relative wall thickness[89], associated to a decreased life expectancy[85]. Not only the risk of ESRD[83] and CKD[96] is increased, but also the women presenting an atherogenic lipid profile[98] including higher levels of triglycerides and cholesterol have a higher risk of CVD later in life[74], especially when associated to higher degrees of severity[76], earlier appearance[101] and increasing probability with each pregnancy[59].

At the present time animal models are extremely important in the identification of placental alterations earlier in pregnancy, in order to evaluate their influence in fetal, cardiac and vascular development. They allowed to understand the association between alterations in the structure and vasculature of the placenta and CHD, but it remains to be seen whether it is overlapping for humans. Newer technologies that will allow an earlier examination of the placenta are essential to obtain histological knowledge of the placenta in order to better understand the association

between placental complications in pregnant women and fetuses with CHD. A close monitoring for development of PE is needed and there is the necessity for preventive measures and new pathways that allow earlier diagnosis and treatment of CHD.

Ethics Committee Approval

N/A

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Author Contributions

Concept – B.F., L.G-M.; Design – B.F., L.G-M.; T.B.; Supervision – L.G-M.; Literature Review - B.F., L.G-M.; Writer - B.F., L.G-M.; T.B.; Critical Review- L.G-M.

Conflicts of Interest

We have no conflicts of interest in this review.

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