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**Feto-maternal indicators of cardiac dysfunction as a justification for the cardiac origins for pre-eclampsia**

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**Abstract**
While the pathophysiology of pre-eclampsia has been postulated as being secondary to placental dysfunction, a cardiac origin has more recently been proposed. Although an association between fetal congenital cardiovascular disease and pre-eclampsia has been demonstrated, no precise pathophysiological mechanism for this association has been described. This review highlights the current biophysical (including echocardiography and Doppler indices) and biochemical (including proteomic, metabolomic and genetic/transcriptomic) markers of cardiac dysfunction that have been investigated in maternal and fetal cardiac disease and their overlap with predictors of pre-eclampsia. Common pathways of inflammatory and anti-angiogenesis imbalance, endothelial damage, and oxidative stress have been demonstrated in both cardiovascular disease and pre-eclampsia and further investigation into these pathways could help to elucidate the common pathophysiological mechanisms linking these disorders.

**KEYWORDS**
biomarker, cardiac, disease, fetal, maternal, pre-eclampsia

**1 | INTRODUCTION**

Hypertensive disorders of pregnancy (HDP) have a major impact on women and their fetuses, affecting up to 10% of pregnancies.¹ The pathogenesis of this umbrella of diseases is not fully understood. While there is an abundance of literature relating to pre-eclampsia screening and prevention based on a placental origin for disease,¹,² there is a paucity of evidence investigating the association between biochemical or biophysical markers for pre-eclampsia and alternative pathophysiological mechanisms, notably those related to maternal and fetal cardiac disease.¹,³ Such variables may have a role in predicting HDP and potentially the risk of fetal or maternal cardiac failure. Hence, we conducted a literature review using standard methodology via PubMed, Medline, CINAHL, EMBASE and Web of Science library databases from inception to February 2023 via the search terms fetal; cardiac; maternal; biomarkers; hypertension and modifications of same.

**1.1 | Origins of hypertensive disorders of pregnancy**

The predominant etiological theory for HDP is early impaired placentation leading to placental insufficiency, oxidative stress and a systemic inflammatory and anti-angiogenic imbalance with subsequent systemic endothelial dysfunction.²,⁴ Such impaired placentation is due to failure of the maternal spiral arteries to remodel correctly, and resultant defective trophoblastic invasion leading to
reduced perfusion across the intervillous space. Histopathologic examination suggests an increased incidence of villous and vascular abnormalities in pre-eclamptic women; however, this is not unique to this condition. In addition, fetal growth restriction (FGR) is a predicted consequence of pre-eclampsia. However in late-onset pre-eclampsia, the fetus can demonstrate normal or exaggerated growth. Placentas displaying stigmata of FGR also have abnormal placental vascular remodeling that is not associated with maternal expression of pre-eclampsia symptoms. This suggests a complex interplay between maternal and fetal factors in the evolution of pre-eclampsia.

A recently proposed theory is that pre-eclampsia originates from a defective maternal cardiovascular system. Women in healthy pregnancy demonstrate significant physiological alterations in cardiac output (CO) and systemic vascular resistance with an increase in the left ventricular (LV) wall mass, LV remodeling and diastolic dysfunction. These physical changes demonstrated on echocardiogram have been recently linked with the angiogenic biomarkers placental-like growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and their ratio. These angiogenic biomarkers have been shown to identify those at high-risk of pre-eclampsia and further highlight the correlation between the maternal cardiovascular state and the uteroplacental unit. Women with recurrent pre-eclampsia demonstrate lower CO and LV mass long-term, increased carotid intima-media thickness and peak mitral filling early diastole/atrial contraction ratio. These changes can be demonstrated later in life with persistent subclinical impairment in LV systolic function. The hypothesis is that pregnancy acts as a "stress test," exposing "at-risk" women through the development of pre-eclampsia. Those who develop pre-eclampsia in any pregnancy are at increased risk in future pregnancies, either due to the inability of their cardiovascular system to recover from the physiological changes due to the pathological process of pre-eclampsia, or their pre-existing predisposition to disease due to the limited cardiovascular reserve (Figure 1).

An assessment carried out in the prediction models for pre-eclampsia is uterine artery Doppler. This is based upon the assumption that inadequate trophoblastic invasion into the spiral arteries influences flow in the uterine arteries, preventing low impedance flow. Other maternal peripheral arteries have been studied, including the ophthalmic artery and brachial artery dopplers which can serve as a predictive test for the development of pre-eclampsia, by way of providing information on the peripheral vascular resistance (PVR). This observation provides further evidence that pre-eclampsia cannot be solely due to inadequate placentation and is likely a systemic maternal maladaptation to pregnancy due to poor cardiovascular reserve.

Genetic and non-genetic risk factors that are associated with pre-eclampsia are also established risk factors for cardiovascular disease (CVD) (Table 1). Eleven factors have been demonstrated to be strongly linked with the development of pre-eclampsia including obesity, chronic kidney disease and cigarette smoking. Others including polycystic ovarian syndrome (PCOS) are linked due to their effects on insulin resistance and insulin like-growth factor respectively which display similar pathological processes to diabetes, another major risk factor for CVD.

Development of HDP places women at increased risk of long-term cardiovascular morbidity and mortality. These women are at a four-fold increased risk of future cardiac failure, and a two-fold...
increased risk for coronary artery disease (CAD), stroke and death, secondary to stroke and CAD. Development of HDP was originally thought to be due to the pathogenesis of pre-eclampsia resulting in injury to the vascular, endothelial and metabolic systems via development of "acute atherosis," with increased lipid deposition demonstrated within the spiral artery walls. Recent research postulates that development of HDP is more likely due to the physiology associated with this patient demographic, suggesting that HDP has its origins in the pre-pregnancy state. Individuals with acquired cardiac disease are at increased risk of developing pre-eclampsia compared with individuals who have congenital heart disease (CHD). However, there is conflicting evidence as to whether the presence of CHD has an effect on the risk of pre-eclampsia compared with the background "low risk" population. The congenital disorders that are most associated with HDP are pulmonary arterial hypertension (PAH) and cardiomyopathy. More research is needed to better determine the link between the maternal cardiovascular system and risk of pre-eclampsia.

Women with a fetus affected by CHD have a seven-fold increased risk of developing early-onset pre-eclampsia in the index pregnancy and two- to three-fold increased risk in subsequent pregnancies. Inversely, infants of a pre-eclamptic pregnancy are much more likely to have a CHD. The structural CHDs that most associated with maternal development of pre-eclampsia are ventricular septal defects (VSD), atrioventricular septal defects (AVSD), double outlet right ventricle (DORV), hypoplastic right heart syndrome (HRHS) and coarctation of the aorta (CoA). The two- or three-fold increased risk in subsequent pregnancies demonstrated to cause defective development of the endocardial cushions and AVSD. The VEGF family, including PlGF, are inhibited by anti-angiogenics, including sFlt-1, which originate from the placenta. Low PlGF, has also been demonstrated to be linked with fetal CHD, namely valvular defects. Increased levels of sFlt-1 and decreased levels of PIGF and VEGF are present in pre-eclampsia and the use of the PI GF/sFlt-1 ratio has been suggested to aid with stratifying patients into low or high risk groups; these biomarkers in particular are, therefore, useful in linking two pathologies that were previously identified to be distinct.

Both structural fetal cardiac disease and fetal cardiac dysfunction are related to maternal pre-eclampsia. Non-immune hydrodrops fetalis (NIHF) is associated with maternal sequelae such as hypertension and generalized edema. The clinical presentation is known as "mirror syndrome" due to the reflective effect of the fetus on the maternal state. The systemic inflammatory response is similar to pre-eclampsia, with the principal discriminating feature being the hemodilution and reduced hematocrit observed in mirror syndrome compared with the hemoconcentration observed in pre-eclampsia. NIHF has been shown to precede pre-eclampsia in approximately 5% of cases and is associated with more severe pre-eclampsia. The pathogenesis of mirror syndrome is poorly understood but is believed to be anti-angiogenic, with increased levels of the anti-angiogenic VEGF-R (receptor) and sFlt-1.

## 2 | MATERNAL ASSESSMENT

Individuals with established cardiac disease constitute a high-risk pregnancy cohort. Such women can be stratified based on different predictive models; the Modified World Health Organization classification as advised by the European Society of Cardiology is the most frequently employed. Monitoring is crucial to detect clinical and subclinical deterioration. Biomarkers in the context of cardiac disease in the pregnant population are less well understood compared to non-pregnant biomarker profiling, but may hold the potential to guide management.

### 2.1 | Maternal biomarkers

**Proteomic**

The main biomarker recommended for evaluation in mothers with pre-existing cardiac disease is the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) with levels of >128 pg/mL at 20-weeks’ gestation predictive of a cardiac event in later pregnancy. NT-proBNP and BNP are "counter-regulatory hormones" released by cardiac myocytes in response to increased wall stress causing LV dysfunction. These biomarkers should remain stable in normal healthy pregnancies but may be raised in those at risk of pre-eclampsia, compared with a low risk population. BNP is increased in individuals with pre-existing cardiac disease. Leucine-rich
α2-glycoprotein-1 (LRG-1) is a biomarker for angiogenesis and inflammation that is more predictive of cardiac failure than BNP.13 Troponin is released in response to myocardial ischemia and necrosis and should only be measured in those with clinical suspicion of ischemia in pregnancy. Cardiac troponins are stable throughout normal pregnancy, with a mild increase in the sensitivity troponins in the early postpartum period, especially in pre-eclampsia.10 A number of other proteomic biomarkers (Table 2) have been investigated in relation to maternal cardiac disease, based on their expression during inflammatory processes and ischemia and their role in plaque destabilization or rupture. The biomarkers that share a role in pre-eclampsia prediction and cardiac disease are highlighted in Table 2.14

Metabolomic

Currently, metabolomic profiles have not been investigated in pregnancies associated with maternal cardiac disease. However, metabolomic studies relating to cardiac disease outside of pregnancy have been performed. Unsurprisingly, elevated levels of lipids, fatty acids and acylcarnitines are associated with increased risk of cardiac disease, namely cardiac failure and ischemia linked to oxidative stress. Elevated levels of amino acids, namely glutamate, have been shown in cardiac disease and inflammatory and cytotoxic death of cardiac myocyte cells.15 These common pathways of oxidative stress and inflammation can be used to highlight the shared links of cardiovascular status and pre-eclampsia.

Transcriptomic/genomic

A meta-analysis investigated the transcriptome of patients with CVD and, separately, that of women with pre-eclampsia, comparing both groups with healthy controls. It demonstrated shared pathways via oxidative stress, inflammation and immune responses between the CVD groups and the pre-eclampsia groups. The common genes and micro-RNAs in the cardiac and pre-eclamptic groups are listed in Table 2.16 The long term cardiovascular effects of pre-eclampsia on the epigenome demonstrate a 50% difference in methylation between monozygous twin pairs discordant for severe pre-eclampsia. Those that exhibit symptoms of HDP have also been shown, by genetic association studies, to have a long-term increased risk of CAD and ischemic stroke.21 This further supports the theory of maternal cardiovascular status playing a role in pre-eclampsia.

2.2 Maternal biophysical markers

Assessment of the maternal cardiovascular status includes measurement of mean arterial pressure (MAP), 12-lead electrocardiogram, and trans-thoracic echocardiogram.6,12,22 In the initial stages of pregnancy, normal physiological changes include dilatation of the systemic vasculature, which plateaus in the second trimester and then increases again for the third trimester and post-partum, reflected in the maternal blood pressure (BP).6 However, in pregnancies where an abnormal pathophysiology response occurs, including cardiovascular pathologies and pre-eclampsia, a highly effective method of diagnosis is measurement of the maternal BP. Due to the interarm difference observed in healthy pregnancies, it has been postulated that the MAP could be a more sensitive method than maternal BP. In patients with pre-existing cardiac disease the advice is to closely monitor BP throughout pregnancy; however, use of MAP for monitoring is not specified.12

It is normal in pregnancy to have an increased LV end-diastolic dimension and LV mass, together with increased left atrial volume and size. Fractional shortening and ejection fraction (EF) should not demonstrate significant change and changes in these parameters can be used to monitor women with known cardiac disease. In those who have valvular disease or cardiomyopathy, it is recommended to repeat the echocardiogram in each trimester or every 1-2 months dependent on the severity of the disease and symptoms.22 Women with pre-eclampsia also have evidence of cardiac dysfunction on echocardiogram, with increased LV wall mass in addition to deteriorating LV diastolic indices.7 The standard measurements taken as part of an echocardiogram are displayed in Table 3.22 More advanced modalities include tissue doppler and speckle tracking echocardiography (STE). Tissue doppler is used to assess changes in the myocardium as an indicator of diastolic dysfunction. Speckles are created when ultrasound bounces off the active myocardium and analysis of this allows for assessment of the myocardial movement.7 STE can be used to assess tissue lengthening, shortening or strain as a more sensitive measure of systolic function, even in those with normal EF (including those with heart failure with preserved ejection fraction [HFpEF] which represents up to 50% of heart failure cases). STE has been shown in pregnancy to be more sensitive than standard echocardiography at assessing subclinical cardiac dysfunction especially in HDP.23

Due to its advantages including accessibility and lack of radiation, echocardiography is the most commonly used imaging modality. However, cardiovascular magnetic resonance imaging (CMRI) can provide a more reproducible, accurate and safe cardiac assessment, especially in cases of aortic pathology.12

Doppler imaging, mainly uterine artery doppler, has been utilized in other parts of the maternal circulation as a method of detecting pre-eclampsia. Measurements from ophthalmic artery dopplers demonstrated utility in pregnancy to determine the patient’s peripheral vascular status.5,6

Another vascular measure of cardiovascular function is arterial stiffness, which has been demonstrated to be increased in patients that have previously suffered from HDP. Arterial stiffness subsequently contributes to the long-term increased risk of cardiac dysfunction. This is due to an increase in central systolic BP which reduces EF, resulting in a decrease in diastolic BP which reduces coronary perfusion and therefore a concurrent increase of pulse pressure.7

These biophysical markers and their associated investigations can help further link the common trends in cardiovascular pathophysiology and HDP.
<table>
<thead>
<tr>
<th>Omic category</th>
<th>Biomarker</th>
<th>Present in maternal cardiac disease</th>
<th>Present in fetal cardiac disease</th>
<th>Present in pre-eclampsia</th>
</tr>
</thead>
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<tr>
<td>Proteomic</td>
<td>BNP</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>NT-proBNP</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>ANP</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>cTnT</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
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<td>cTnI</td>
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<td>X</td>
<td>X</td>
</tr>
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<td></td>
<td>LRG-1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>GDF 15</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
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<td>H-FABP</td>
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<td>X</td>
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<td>PIGf</td>
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<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>s-Flt1</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>s-Eng</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PAPP-A</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>TGFβi</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Gelsolin</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>LMNA, FLNA, TPM4, ACTG1</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>(cytoskeleton proteins)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBEGF-like GF</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Metabolomic lipids</td>
<td>Acylcarnitine</td>
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<td>X</td>
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<tr>
<td></td>
<td>Fatty acid</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Phospholipid</td>
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<td>X</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Homocysteine</td>
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<td></td>
<td>X</td>
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<tr>
<td></td>
<td>S-adenosylhomocysteine</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Oxidized glutathione</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Methionine</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>N-acetylcarnosine</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uric acid</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>4-Hydroxybenzeneacetic acid</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>5-Trimethylsilyloxy-n-valeric acid</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Propanoic acid</td>
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<td></td>
<td>X</td>
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<tr>
<td></td>
<td>Hydracrylic acid</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Transcriptomic/</td>
<td>miR-1</td>
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<tr>
<td>epigenetic</td>
<td>miR-19</td>
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<td>X</td>
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<td></td>
<td>miR-21</td>
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<td></td>
<td>miR-22</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td></td>
<td>miR-29a</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td></td>
<td>miR-29c</td>
<td>X</td>
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<td></td>
<td>miR-99a</td>
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<td>miR-126</td>
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<td>X</td>
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<td>miR-145</td>
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<td>miR-196a</td>
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</tr>
<tr>
<td></td>
<td>miR-181</td>
<td>X</td>
<td></td>
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</tbody>
</table>

(Continues)
While the primary focus for pre-eclampsia prediction has been maternal variables, the fetus must also be considered as a contributor as there is a link between fetal CHD and maternal pre-eclampsia.\(^9,11\) Assessment of the fetal heart is complex and involves assessment of cardiac structure and function. It is crucial to identify deterioration of fetal cardiac function and development of cardiac failure to improve outcome and management as fetal cardiac failure is associated with a poor prognosis. The cardiovascular profile score (CPS) is a useful scoring system to identify markers of deterioration of fetal cardiac function (Figure 2). Those fetuses that are at increased risk of developing cardiac failure in utero include those with fetal arrhythmia, fetal anemia (alpha-thalassemia, parvovirus B19, twin anemia-polycythemia sequence), non-anemic volume load (TTTS, arteriovenous malformations and sacrococcygeal teratoma), increased afterload (FGR and outflow tract obstruction), intrinsic myocardial disease (cardiomyopathy), CHD and external cardiac compression.\(^24\) Early detection is key for both fetal management and prediction of the potential effects on the mother, including increased risk of pre-eclampsia.\(^3\) Biomarkers in maternal blood, amniotic fluid and cord blood have been investigated to determine their usefulness as predictive tools.\(^17\)

### Table 3 - Typical cardiac indices measured in a standard echocardiogram.

<table>
<thead>
<tr>
<th>Cardiac indices</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diastolic indices</strong></td>
<td>E wave, A wave, isovolumic contraction time, ejection time, isovolumic relaxation time, E/A ratio, left atrial volume, peak velocity of early diastolic mitral annular motion (e'), peak velocity of late diastolic mitral annular motion (A'), peak velocity of systolic mitral annular motion (S')</td>
</tr>
<tr>
<td><strong>Systolic indices</strong></td>
<td>Left ventricular outflow tract velocity time integral, cardiac index, myocardial performance index, stroke volume, ejection fraction, global circumferential strain, global longitudinal strain</td>
</tr>
</tbody>
</table>

Source: Adapted from reference [22].

### 3 | Fetal Assessment

While the primary focus for pre-eclampsia prediction has been maternal variables, the fetus must also be considered as a contributor as there is a link between fetal CHD and maternal pre-eclampsia.\(^9,11\) Assessment of the fetal heart is complex and involves assessment of cardiac structure and function. It is crucial to identify deterioration of fetal cardiac function and development of cardiac failure to improve outcome and management as fetal cardiac failure is associated with a poor prognosis. The cardiovascular profile score (CPS) is a useful scoring system to identify markers of deterioration of fetal cardiac function (Figure 2). Those fetuses that are at increased risk of developing cardiac failure in utero include those with fetal arrhythmia, fetal anemia (alpha-thalassemia, parvovirus B19, twin anemia-polycythemia sequence), non-anemic volume load (TTTS, arteriovenous malformations and sacrococcygeal teratoma), increased afterload (FGR and outflow tract obstruction), intrinsic myocardial disease (cardiomyopathy), CHD and external cardiac compression.\(^24\) Early detection is key for both fetal management and prediction of the potential effects on the mother, including increased risk of pre-eclampsia.\(^3\) Biomarkers in maternal blood, amniotic fluid and cord blood have been investigated to determine their usefulness as predictive tools.\(^17\)

### 3.1 | Fetal biomarkers

#### Proteomic

The most widely researched fetal biomarkers are proteins also used to assess adult cardiac failure and include the natriuretic peptides; atrial (ANP), BNP and NT-proBNP. ANP and BNP correlate with the severity of cardiac failure when analyzed in cord blood. Raised NT-proBNP has also been shown to correlate with more severe cardiac failure in utero.
in conjunction with a worsening CPS in fetuses with CHD, arrhythmias or both, potentially due to increased central venous pressure.17

Studies have also been used to investigate whether biomarkers can distinguish types of CHD. One such study identified a reduction in the maternal expression of the protein gelsolin in pregnancies associated with fetal conotruncal defects. Gelsolin is responsible for the downregulation of the proinflammatory immune response in pregnancy and is reduced, along with other members of the cytoskeleton family, in pregnancies that develop pre-eclampsia or those associated with a fetal CHD (Table 2).18

Metabolomic

A systematic review by Mires et al. conducted a comprehensive review of metabolomics and CHD.19 Measurement of the maternal metabolites have shown that the acylcarnitines, fatty acids and phospholipids that are reduced in pregnancy, are lower in those with fetal CHD compared with controls. Homocysteine, one of the metabolites of methionine an essential amino acid, is elevated in pregnancies with fetal CHD due to disruption of the homocysteinemethionine cycle. Homocysteine creates several metabolites that are involved in the oxidative stress pathway, which is also linked to the pathophysiology of pre-eclampsia.19 The research into metabolites and fetal CHD is still relatively novel and warrants further study.

Transcriptomic/epigenetic

Studies into transcriptomic factors, miRNA’s and epigenetic factors involved in cardiogenesis have elicited some biological pathways that may help with understanding congenital cardiac disease, but still require further investigation. Epigenetic studies of CHD have highlighted some potential biomarkers, including aberrant CpG methylation patterns and histone modifications; however, further investigations are needed.20

3.2 | Fetal biophysical markers

Fetal structural assessment includes two-dimensional imaging of the cardiac structure, rhythm assessment, color and pulsed flow doppler assessment, and ventricular functional parameters. Functional assessment of the fetal heart is also useful to direct management. Evaluation of systolic function in the fetal heart includes measuring EF, shortening fraction, CO and volume and maximal displacement of the valve ring or tricuspid annular plane systolic excursion (TAPSE). Speckle track echocardiography (STE) has become an additional modality in assessing fetal cardiac strain; however, it is not currently routinely used in clinical practice but can give information on subclinical ventricular dysfunction. The evaluation of the EF and shortening fractions are important assessments of the pumping function. Evaluation of diastolic function includes measuring the blood flow through the atioventricular valves, pulmonary vein and ductus venosus by both spectral and tissue doppler imaging.25 These require a combination of M-mode, 2D and 3D doppler and imaging. Myocardial performance index can also be tested as a marker of global ventricular function applied to either or both ventricles and is reliable and reproducible.24

Another recommended assessment of cardiac function is CPS24 (Figure 2). The CPS includes interrogation of venous and arterial doppler. Arterial doppler of fetal middle cerebral, fetal descending aorta and maternal uterine and umbilical arteries, provide useful information on the assessment of the fetal and placental PVR. Venous doppler allows for assessment of the fetal preload, cardiac function and central venous pressure via measurement of the ductus venosus, umbilical vein, inferior vena cava and hepatic veins.25 These are useful investigations in conjunction with the structural assessment of the fetal heart.

4 | CONCLUSION

Studies that elucidate the maternal and fetal biochemical and biophysical markers for cardiac disease lend weight to the hypothesis
that the origins of pre-eclampsia are cardiac. Maternal pre-eclampsia, cardiac disease and fetal cardiac disease are significant contributors to fetal and maternal morbidity and mortality. Future research into prediction and prevention of these conditions will increase our understanding of the link between these diseases. As described, the pathways underlying pre-eclampsia; namely inflammatory, oxidative stress and anti-angiogenic, demonstrate established links with maternal cardiac disease and fetal cardiac disease. Therefore, further investigation into these and the biomarkers involved should provide the knowledge required to improve understanding and detection of these significant pregnancy-specific conditions.

**AUTHOR CONTRIBUTIONS**

Kelly M. Reilly and Fionnuala Mone are responsible for conception and design of the study with input from all remaining authors. Kelly M. Reilly is responsible for the text with contributions from all remaining authors. Final review and approval by all authors.

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**CONFLICT OF INTEREST STATEMENT**

MR, JW, MJK were employed by Randox Laboratories Ltd and hold no shares. PF is the Managing Director and owner of Randox Laboratories Ltd.

**DATA AVAILABILITY STATEMENT**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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**REFERENCES**


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