Maternal Cardiovascular Involvement

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Measurement of Cardiac Function

The measurement of cardiac indices is important in understanding the maternal haemodynamic changes that occur in both physiological and pathological states of pregnancy. Traditionally, the invasive Swanz Ganz pulmonary artery catheter was the gold standard for measuring cardiac function. However, non-invasive transthoracic echocardiography has shown excellent correlation with these invasive techniques and as a result has become an equivalent gold standard [1].

More recently, there has been increasing interest in the use of other non-invasive cardiac monitors such as Ultrasound Cardiac Output Monitor (USCOM®), Non-invasive Cardiac Output Monitor (NICOM®) and an inert gas rebreathing method (INNOCOR®). The main advantage of these monitors is that healthcare professionals with different levels of experience can use them as point-of-care systems to assess cardiac function. Various studies have validated these cardiac monitors in non-pregnant individuals and have shown good reproducibility and correlation with echocardiograms and pulmonary artery catheterisation [2, 3]. Furthermore, studies in pregnancy have also demonstrated a reasonable correlation between the USCOM and NICOM cardiac output monitors when compared with echocardiography [4, 5].

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Echocardiograms Explained: What Information Can You Obtain?

Heart rate and rhythm, cardiac output, and stroke volume

Valvular morphology and function

Cardiac morphology

This is valuable in assessing atrial and ventricular dilation, and concentric and eccentric ventricular hypertrophy. Left ventricular hypertrophy is measured through the thickness of the inter-ventricular septum and posterior left ventricular wall.

Systolic function

This can be evaluated through assessing stroke volume, cardiac output and left ventricular ejection fraction. Measurement of myocardial contractility is also valuable in assessing systolic function.

Diastolic function

This is evaluated through measuring the flow across the mitral valve during diastole as well as through assessment of left atrial size and volume. Diastolic dysfunction is an important factor in cardiovascular disease and often precedes systolic dysfunction. It is characterized by:

1. Increased left atrial size
2. Increased isovolumetric relaxation time (IVRT): this is the time between closure of the aortic valve at the end of systole and the opening of the mitral valve at the beginning of diastole, i.e. the time taken to build an adequate pressure gradient between the left atrium and ventricle.
3. Abnormal E/A ratio: the E/A ratio is a measurement of flow through early and late diastole. Due to the large pressure gradient, early diastole is characterized by rapid flow across the mitral valve resulting in a peak in flow called the E wave. The "a wave" is a reflection of increased filling velocities in late diastole due to an atrial contraction.
4. Prolonged Deceleration time: the deceleration time refers to the interval between the peak of the E wave and the beginning of diastasis. Diastasis refers to the period where flow across the mitral valve decreases as a result of rising ventricular pressures.
5. Increased E/e' ratio: this refers to the ratio of flow across the mitral valve through early diastole (the E wave) and the mitral annular early diastolic velocity (e' wave). This is reflective of increased atrial pressures.

Measurement of Vascular Function

Peripheral arterial measurements are also valuable in assessing physiological and pathological changes of pregnancy. Pregnancy is characterized by vascular remodelling across the entire arterial tree. In general, the physiological changes within this vasculature are designed to increase flow so as to allow for greater

perfusion of the uteroplacental unit. Vascular function is predominantly assessed through measurement of arterial stiffness across the aortic, brachial, carotid, ophthalmic and uterine arteries. The main measures of arterial stiffness include:

1. Central and brachial blood pressure—traditional measurements of blood pressure are performed at the brachial artery. Systolic pressures, however, vary through the arterial tree, and more recent studies have shown that arterial pressures measured at the level of the aorta (central BP) are better correlated with cardiovascular events [6]. In pregnancy, while both brachial and central blood pressures decrease with gestation, central BP appears to have a more pronounced decline [7].
2. Augmentation index (AIx)—the augmentation index is a measure of systemic arterial stiffness and can indicate left ventricular workload and endothelial function [8]. This index is a reflection of the components of blood pressure and is made up of two discrete parts. The first component is forward flow and encompasses the blood that is pumped out from the heart into the bloodstream at the point of measurement. The second component is the backward flow that occurs due to the reflected wave of blood. As a result of changes in arterial calibre, arterial pathway and vessel plaques through the arterial tree, some proportion of blood flow is reflected back up the arterial tree and forms this reflected wave [9]. The augmentation index is the percentage of pulse pressure due to the reflected wave. Through the use of non-invasive blood pressure equipment, the arterial waveform, central blood pressure and central augmentation pressure can be detected [9]. These non-invasive techniques have been well validated in catheterization laboratories [9]. While the AIx remains within the normal range throughout pregnancy, it does show a slight decrease over the first two trimesters before increasing towards term [8].
3. Pulse wave velocity (PWV)—"PWV is defined as the velocity at which the pressure waves, generated by the systolic contraction of the heart, propagate along the arterial tree" [10]. Practically, it is measured over the carotid and femoral arteries through the use of non-invasive pressure sensors to measure arterial tonometry [11]. Measurement of PWV is considered the gold standard for assessing arterial stiffness and is inversely proportional to arterial elasticity and compliance [11]. PWV follows a similar course to AIx through pregnancy [8].

Normal Cardiovascular Adaptation to Pregnancy

Cardiac Output, Stroke Volume and Heart Rate

Cardiac output rises steadily through pregnancy, increasing to a maximum of 30–50% above non-pregnant values near term (Fig. 15.1) [13]. The sharpest rise incardiac output occurs in the first 8 weeks of gestation with a continued increase throughout the second trimester [13]. The rise in cardiac output is a result of an interplay between factors affecting preload and afterload including:

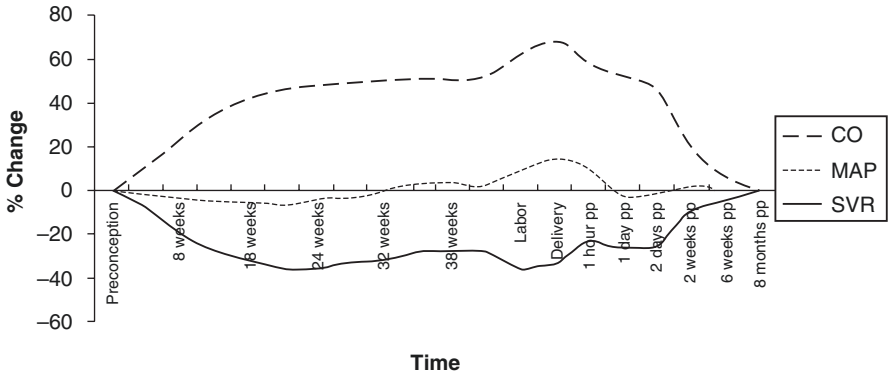

Fig. 15.1 Haemodynamic changes in pregnancy, labour and postpartum. Time on the x-axis changes scale. (Adapted from the Cornette and Roos-Hesselink [12], with permission from Springer). CO cardiac output, MAP mean arterial pressure, PP postpartum, SVR systemic vascular resistance

(a) Increased blood volume—this results in a rise in left ventricular preload, which can be assessed through measuring left atrial diameter and left ventricular end-diastolic dimensions [14].
(b) Drop in systemic vascular resistance—this is largely a reflection of vasodilation and results in a decrease in afterload [14].
(c) Increased maternal heart rate—resting heart rate increases by 10–30 beats per minute, reaching a peak in the third trimester. While in early pregnancy the rise in cardiac output is mainly related to a rise in stroke volume, in later pregnancy, this rise in heart rate plays a larger role [14].

Contractility, Ejection Fraction and Cardiac Remodelling

The haemodynamic changes in pregnancy create a state of volume overload, which results in *temporary* eccentric cardiac remodelling and left ventricular hypertrophy [15]. Studies have shown that the left ventricular wall thickness and mass increase by 28% and 52%, respectively [16]. Despite these changes, cardiac contractility, and right and left ventricular ejection fraction are preserved in pregnancy [15].

Blood Pressure and Systemic Vascular Resistance

During pregnancy, systemic vascular resistance (SVR/TVR) drops to 30% below non-pregnant values. SVR declines throughout pregnancy, reaching a trough in the early third trimester (Fig. 15.1) [15]. The drop in SVR contributes to a decrease in arterial pressures, which reach a nadir in the second trimester (a drop of 5–10 mmHg)

[17]. Mean arterial pressure (MAP) begins to rise in the third trimester and returns to non-pregnant levels in the puerperium [17].

These changes to blood pressure and SVR are mediated by a rise in oestrogen, progesterone, nitric oxide and relaxin [16]. Furthermore, the decrease in SVR can also be attributed to trophoblast invasion of the spiral arteries and the subsequent drop in uteroplacental resistance. In fact, some studies have suggested that this contributes to 20–26% of the reduction in SVR in the second trimester [18].

Changes in Blood Volume

The vasodilation and drop in SVR in pregnancy cause activation of the renin-angiotensin-aldosterone system, which in turn increases circulatory volume [16]. As a result, plasma volume increases by 40–45%, reaching a peak at 30–34 weeks' gestation [16]. This rise in plasma volume has an important role in maternal haemodynamics as it (1) contributes to the rise in preload, which plays an important role in increasing cardiac output, (2) facilitates the delivery of nutrients and removal of waste products from the uteroplacental unit, and (3) provides a reserve for blood loss during delivery. Due to an increase in plasma erythropoietin levels, red blood cell mass also rises in pregnancy to 15–20% above non-pregnant levels [19]. This helps support the higher oxygen requirement of pregnancy. As the increase in red blood cell mass is lower than the rise in plasma volume, a dilutional anaemia ensues [16].

The Role of Maternal Haemodynamics in the "Placental Syndromes" of Pre-eclampsia and Fetal Growth Restriction

PE and FGR are conditions that are thought to arise from the common pathological pathway of placental dysfunction. The underlying mechanisms leading to placental dysfunction and contributing to these "placental syndromes" are likely multifactorial and the focus of much debate. Traditionally, it has been hypothesized that impaired fetal growth and placental insufficiency are a product of inadequate trophoblast invasion, causing incomplete remodelling of the spiral arteries and the persistence of a high resistance placental vascular bed. This results in placental ischaemia-reperfusion injuries and poor fetal perfusion, which thereby impairs fetal growth. Placental ischaemia also triggers the release of anti-angiogenic factors into the maternal circulation. This causes an imbalance of pro-angiogenic and anti-angiogenic factors, resulting in endothelial dysfunction and the subsequent clinical manifestations of PE (Fig. 15.2) [20, 21]. Predictive models for PE and FGR use markers of placental function such as uterine artery Dopplers, PAPP-A and PlGF. While these markers have shown promise in predicting early-onset disease, their value in late-onset FGR and PE is somewhat limited. Thus, while the placental hypothesis is likely central to the pathogenesis of FGR and PE, it does not explain

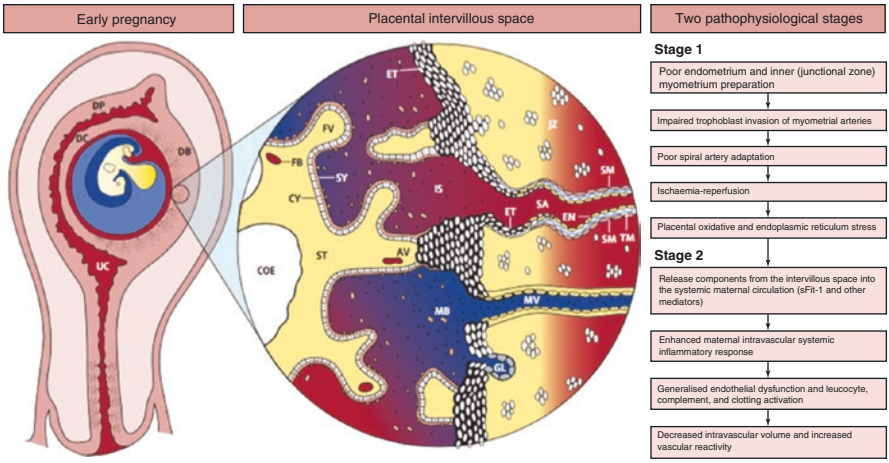

Fig. 15.2 Possible pathophysiological processes in pre-eclampsia. (Figure adapted from Steegers et al., with permission from Elsevier [21]). AV anchoring villus, COE coelomic cavity, CY cytotrophoblast, DB decidua basalis, DC decidua capsularis, DP decidua parietalis, EN endothelium, ET extravillous trophoblast, FB fetal blood vessel, FV floating villus, GL gland, IS intervillous space, JZ junctional zone myometrium, MB maternal blood, leaving the intervillous space with various components such as anti-angiogenic factors. MV maternal vein, SA spiral artery, SM smooth muscle, ST stroma, SY syncytiotrophoblast, TM tunica media, UC uterine cavity, sFlt-1 soluble form of the vascular endothelial growth factor receptor

the entire picture, and perhaps, this has hampered the ability to predict and prevent the outcomes of these complex disease processes.

More recently the role of the maternal circulation in the pathogenesis of FGR has received greater attention. While there are some differences between studies, a common finding is that in comparison to normal pregnancies, FGR is associated with a less dramatic rise in maternal heart rate, stroke volume and cardiac output. Furthermore, women whose pregnancies are complicated by FGR display higher mean arterial pressures and total vascular resistance and an element of both systolic and diastolic dysfunction. These markers of cardiovascular function have been examined in both the preclinical and clinical phases of FGR.

Cardiac Output, Stroke Volume and Heart Rate

Various studies have shown a lower heart rate, stroke volume and cardiac output in pregnancies complicated by FGR when compared to uncomplicated pregnancies [22–24]. Interestingly, the lower stroke volume and cardiac output appear to correlate with a smaller end-diastolic volume and left atrial diameter [25]. This suggests that this relatively smaller rise in stroke volume and cardiac output is a result of inadequate plasma volume expansion and thus a lower preload [25, 26]. Supporting this hypothesis are the findings of lower renin, angiotensin and aldosterone (RAAS) levels in women with PE and FGR [27, 28]. These hormones

play a key role in regulation of plasma volume and blood pressure. Furthermore, studies have reported these disparities in cardiovascular adaptation as early as 5–8 weeks' gestation, suggesting that such haemodynamic maladaptation precedes the clinical manifestations of FGR [29, 30]. As a result, cardiovascular markers have shown some promise as screening tools, particularly in the high-risk population [30, 31]. However, further research into the predictive value of these cardiac indices is required.

Mean Arterial Pressures and Total Vascular Resistance

Studies have consistently shown that maternal total vascular resistance (TVR) and mean arterial pressures are higher in pregnancies complicated by FGR [1, 25, 32]. The rise in systolic and diastolic blood pressures, and TVR is not only independent of concomitant hypertension or PE but also appears to precede the clinical phase [18, 32]. This suggests at least some element of causality. In fact, TVR can be used as a predictive marker for "placental syndromes of pregnancy" [18]. Vasapollo et al. showed that, in high-risk pregnancies, TVR >1400 dynes at 24 weeks' gestation has a 89% sensitivity, 94% specificity, 77% positive predictive value (PPV) and 97% negative predictive value (NPV) for predicting the likelihood of a pregnancy complicated by a "placental syndrome". In this particular study, TVR performed better than the standard uterine artery Doppler indices currently used for predicting pregnancy complications [18]. However, further research is required to confirm the value of TVR as a screening tool in the general obstetric population.

Cardiac Morphology and Remodelling

The findings of abnormal cardiac remodelling in FGR pregnancies have been reported some decades ago. Scandinavian studies from the 1960s have shown that women with smaller heart volumes are at a higher risk of delivering small for gestational age infants [33]. More recent echocardiographic studies have shown that FGR pregnancies are characterized by smaller left atrial diameters, left ventricular outflow tracts and left ventricular diastolic dimensions [25, 29, 34, 35]. Pregnancies complicated by "placental syndromes" have also been associated with a depressed left atrial function and altered concentric hypertrophy of the left ventricle, in contrast to the eccentric hypertrophy that normally takes place [18]. The underlying causes of this maladaptation may be attributed to a number of factors. Firstly, the smaller left atrial diameters and diastolic volumes are suggestive of decreased preload [25]. This may be a result of inadequate compensation to the vasodilation and decreased intravascular volume seen in early pregnancy [26]. Secondly, the concentric left ventricular hypertrophy is likely a reflection of the pressure overload that is characteristic of "placental syndromes" of pregnancy [36]. This is in contrast to the volume increase seen in physiologically normal pregnancies accompanied by eccentric left ventricular hypertrophy.

Diastolic Dysfunction

There is significant disparity between studies with regard to diastolic dysfunction in the "placental syndromes" of pregnancy. Some echocardiographic studies have suggested an element of diastolic dysfunction in pregnancies complicated by FGR and PE, demonstrating a decreased E/A ratio and longer isovolumetric relaxation time [22, 34, 35]. This suggests mild diastolic dysfunction and impaired relaxation of the left ventricle [22, 34, 35]. However, this has been contradicted in other studies [25] where no difference has been identified in diastolic function between FGR and normal pregnancy population groups. Further research with larger sample cohorts is required to clarify these findings.

Vascular Dysfunction

The association between vascular dysfunction and "placental syndromes" of pregnancy has received somewhat less attention than the heart. The few studies within this area have mainly focused on PE rather than FGR and have shown a positive correlation between PE and arterial stiffness (increased central BP, PWV and AIx) [37, 38]. Such vascular remodelling is evident in the carotid artery, which has proven to be a well-established marker for cardiovascular morbidity and mortality [38]. These changes in arterial function appear to precede the clinical phase of the disease. When used in the first trimester, in addition to maternal history in the screening for PE, these indices improve the detection rate significantly from 33% to 43% at a 5% FPR [37]. However, the overall low detection rate renders the changes in arterial function a poor predictive tool. There is a paucity of research examining vascular remodelling in FGR with these studies showing conflicting results [39, 40].

The relationship between "placental syndromes" and vascular dysfunction has also been examined through assessment of cerebral vasculature. The ophthalmic and middle cerebral artery Doppler studies are thought to reflect hyperperfusion of the central nervous system (CNS) as a result of endothelial dysfunction. Supporting the CNS hyperperfusion hypothesis are various studies, which have shown that FGR and PE patients exhibit lower ophthalmic artery resistance, that is, an increase in vascular flow [41–43]. While these findings again predate the clinical phase of the disease, the predictive value of the ophthalmic artery Doppler requires further evaluation [42, 44, 45].

Issues with the Cardiac Hypothesis

Inconsistent Study Results

The discrepancy between studies examining maternal cardiovascular changes in FGR pregnancies can be attributed to two main reasons:

1. Definition of the population group: studies that include small for gestational age fetuses and neonates as a marker of FGR tend to show less dramatic differences between cases and controls. However, when FGR is defined by fetal weight, abdominal circumference and abnormal umbilical artery Doppler indices, there are more drastic differences between population groups. The latter method is more representative of the pathological process of FGR, while fetuses that are constitutionally small confound the former.
2. Sample size: the majority of studies in this research area have a small sample size and are likely underpowered to detect a difference between population groups. Larger prospective studies and meta-analyses are required in order to better identify the trends in cardiovascular function in FGR and PE.

The Uncertainties Around Cause Versus Effect, and Early Versus Late FGR

It is unclear whether cardiovascular maladaptation causes or is the result of uteroplacental dysfunction. Pregnancy is a physiological stress test. Cardiovascular maladaptation may therefore be a reflection of failing this stress test, and the resultant impaired fetal perfusion and fetal growth restriction are just symptoms of underlying cardiovascular dysfunction. Alternatively, it is also plausible that cardiovascular maladaptation is itself a symptom of a poorly functioning uteroplacental unit and abnormal placentation. Lastly, it may be the failure of both processes that manifests in "placental syndromes". Defective placentation results in a high-resistance placental bed, which causes changes in the maternal cardiovascular system. However, not everyone with abnormal placentation develops PE or FGR. One way to explain this contradiction would be to surmise that the clinical syndrome develops only in those unable to undergo the necessary cardiovascular adaptations in response to defective placentation. All three of these hypotheses currently remain conjecture, and hopefully longitudinal studies including the pre-pregnancy period will clarify this issue.

It has also been proposed that early- and late-onset FGR represent separate pathological processes, and perhaps cardiovascular maladaptation may explain the differing pathologies [46]. There is a strong consensus that early-onset FGR is a result of true placental insufficiency. Supporting this, the current screening methods of low PAPP-A and raised uterine artery Dopplers can reliably predict early-onset disease. However, 70–80% of cases of FGR are defined as late onset, and within this population group, these placental markers are of modest value [47]. It has thus been proposed that such late-onset disease is not a result of true placental insufficiency but rather the inability of the maternal cardiovascular system to meet the increasing demands of pregnancy [46]. There is certainly evidence that placental histology is different between early- and late-onset FGR, with the former reflecting abnormal placentation and ischaemia and the latter reflecting more heterogeneous changes [48]. Supporting these findings is also evidence of lower cardiac output and higher TVR in pregnancies complicated by late-onset FGR [24].

The single largest risk factor for stillbirth is undiagnosed fetal growth restriction [49]. Perhaps, through a better understanding of the role of maternal haemodynamics in the pathogenesis of early- and late-onset FGR, we will be able to better predict and monitor the population groups at risk of what is essentially a preventable adverse outcome.

Long-Term Cardiovascular Implications of Fetal Growth Restriction to the Mother

Placental syndromes of pregnancy are associated with long-term maternal cardiovascular sequelae. Studies have shown that mothers with FGR infants have a two-fold increased risk of cardiovascular disease and cardiovascular disease-related deaths [50, 51]. These findings have also been replicated in the pre-eclamptic population [52, 53]. Mothers of FGR infants have also been shown to have higher rates of glucose impairment, abnormal lipids, persistent endothelial dysfunction and evidence of subclinical atherosclerosis [54, 55]. It is unclear whether this vascular impairment is a result of PE and FGR causing a permanent vascular insult, or a reflection of underlying cardiovascular dysfunction in this population group in the first place. Nonetheless, it does appear that these women could benefit from closer long-term follow-up and risk modifications for prevention of cardiovascular disease.

Key Points

- Adequate cardiovascular adaptation is essential to meeting the metabolic demands of the mother, fetus and uteroplacental unit. Cardiovascular changes in pregnancy include a drop in total vascular resistance; a rise in stroke volume, heart rate and cardiac output; a significant expansion of blood volume; and temporary eccentric remodelling of the heart.
- Evidence suggests that pregnancies complicated by FGR are associated with cardiovascular maladaptation. Mothers of FGR fetuses have been shown to have a higher systemic vascular resistance and a lower stroke volume and cardiac output in comparison to normal pregnancies.
- It is unclear whether such maladaptation is the cause or the result of abnormal placentation or whether it is a combination of both pathological processes that results in the clinical phenotype of FGR.
- The cardiovascular maladaptation associated with FGR appears to predate the clinical phase of the disease, and as such, cardiovascular indices may have a role in predicting early- and late-onset FGR. Further research is required to explore and validate the use of these markers in predictive models.

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