HYPOTHESIS

MATERNAL CARDIAC TWIST PRE PREGNANCY: POTENTIAL AS A NOVEL MARKER OF PRE-ECLAMPSIA

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SUMMARY

Preeclampsia (PE) is a complication during pregnancy associated with cardiovascular dysfunction and ensuing maternal and perinatal mortality and morbidity (1). The pathogenesis of the disease is unclear, and it is possible that otherwise healthy women may be predisposed to its development prior to pregnancy (2). During healthy pregnancy, the cardiovascular system is stressed in a similar fashion to that seen during exercise in non-gravid females. We hypothesise that cardiovascular assessment at rest and during moderate exercise in the pre-conception period will establish if the developmental origins of PE exist prior to gestation.

BACKGROUND

Cardiovascular function during normotensive vs. pre-eclamptic pregnancy

Healthy pregnancy is characterised by progressive physiological adaptation of the maternal cardiovascular (CV) system that facilitates optimal foetal development. The adaptations that constitute a healthy or normal progression are not always evident, and in particular, CV adaptation to pregnancy is highly individualised. Some women develop pregnancy-related CV dysfunction such as preeclampsia (PE). Typically, PE is diagnosed by the development of hypertension and proteinuria after 20 weeks of pregnancy (3, 4) and is the leading cause of maternal and perinatal mortality and morbidity (1). Despite continued efforts to improve the understanding of the aetiology and pathophysiology and subsequently, treatment for the disease, cardiovascular changes in PE are not well understood. Preeclampsia before 34 weeks (early onset PE) is believed to differ in pathogenesis from late onset PE (>34 weeks) and can be characterised by a haemodynamic profile of increased systemic vascular resistance (SVR) and lower cardiac output (CO). Early onset PE is more often associated with uteroplacental insufficiency and significant adverse maternal and perinatal outcomes. In contrast, late onset PE (>34 weeks) involves an increased CO and lower SVR and is less likely to be associated with uteroplacental insufficiency and adverse perinatal outcomes (5). It is not known if PE develops secondary to the cardiovascular maladaptation in pregnancy or if a pre-existing cardiovascular dysfunction predisposes some women to develop PE (6). Screening, diagnosis and

disease management would be vastly improved if more were known about the onset of the maladaptive process associated with PE. To date, a combination of maternal factors including medical history, body mass index (7), age, parity (8) and blood pressure (BP) (3, 9) have been used to predict the development of PE. In the first trimester, arterial stiffness is significantly increased in women who develop PE (9). Current hypotheses speculate that cardiovascular dysfunction is evident very early in pregnancy in PE (2, 6) and precedes the clinical manifestation at a later stage but whether cardiovascular dysfunction is present before pregnancy remains to be elucidated.

The potential of left ventricular twist

During left ventricular (LV) contraction, the human heart muscle undergoes complex deformation. This deformation is caused by the heart muscle's specific anatomical form (10) and results in a wringing motion, termed LV twist. This motion improves the efficiency of cardiac function, distributes myofibre stress evenly across the chamber's muscle and may be sensitive to subtle sub-clinical changes in cardiac function prior to the development of overt disease (11-13). A recent study has shown that LV twist was significantly reduced in one of two groups of young male individuals (14). Importantly, there were no differences in cardiac structure, heart rate or arterial haemodynamics between these groups. These data suggest that even in otherwise healthy individuals without overt cardiovascular abnormalities, differences in LV twist may be present. This highlights the potential of LV twist to be used as a sensitive early marker of altered cardiac function in the absence of gross changes in LV structure or haemodynamics. In addition, because of its sensitivity to loading conditions and contractile state (15-19) – both which are altered during pregnancy as a consequence of raised blood volume (20) and myocardial contractility (21) - measuring LV twist will reflect not only the local changes in cardiac function but also in part respond to differences in the haemodynamics between women. Only few studies have examined LV twist (22) and other markers of LV deformation such as LV strain (21, 23, 24), during pregnancy and to date no data exist from pre-eclamptic women or in pre-pregnancy. Thus, at pre-conception, it may be possible to identify women with altered LV twist, strain and preload / afterload which may be an early predictor of pregnancy-related complications such as PE. Moreover, LV twist can be assessed in the non-pregnant

and pregnant woman during exercise, which allows for the quantification of 'twist reserve' and thereby provides insight into the integrated, dynamic adjustment of the pre-pregnancy cardiovascular system to enhanced cardiovascular demand.

Role of exercise testing

Pregnancy has been described as a continuous physiological stress test for the maternal CV system (25). The pregnant woman's body is permanently exposed to a changing physiological environment and thus disturbance of homeostasis. Consequently, acute adjustments of all integrated systems are required. From a cardiovascular perspective, adequate responses are not only necessary to provide an enhanced blood flow to the mother and the foetus; rapid acute adjustments are also pivotal to prevent excessive stress on the heart and arteries (26). While not directly comparable, acute exercise alters the magnitude of cardiac loading conditions and arterial haemodynamics similarly to that observed during the second and third trimester of pregnancy (e.g. increased CO, reduced SVR, BP, end-diastolic volume / preload and stroke volume) (23, 27, 28). In comparison, a differing haemodynamic pattern of increased SVR and lower CO occurs in early-onset PE, and a reduced SVR and higher CO in late-onset PE (5, 25). Therefore, challenging the non-pregnant woman's cardiovascular system acutely by exercise may mimic similar cardiovascular response and provide an early insight into the ability to adjust to the cardiovascular stress of pregnancy. Previously, LV twist has been shown to increase acutely during exercise in healthy non-pregnant women (27), and has been minimally researched at rest in healthy pregnancy (21, 22, 29), but the relationship of LV twist and PE has not been explored. While it is unlikely that initial tests will be able to predict and differentiate between possible pregnancy complications, it may be possible to detect maternal factors that predispose the development of PE in the pre-conception period. A series of comprehensive investigations will be required to provide more precise information and maybe ultimately normal reference values for optimal pre-pregnancy cardiovascular function and concerted efforts from research collaborations will be required to achieve this long-term aim.

HOW THE HYPOTHESIS MIGHT BE TESTED

i) A thorough preconception assessment is necessary to identify the origin and onset of development of CV maladaptation to pregnancy. Mahendru *et al.* (30) have demonstrated successful recruitment at preconception. Whilst there are significant difficulties associated with the recruitment of participants, including cohort size, infertility and pregnancy loss following implantation, the collection of data prior to pregnancy is imperative to understand the origins and the development of the different pathogenic isoforms of PE. Mahendru *et al.*'s study was strengthened by the longitudinal design, and adequate sample size to show statistical power, increasing the confidence that preconception assessment – when done well – can be successful.

ii) Despite advances in diagnostic testing, assessment of the response of CV parameters to exercise is still understudied. Previous studies have demonstrated the potential of exercise testing to unmask abnormalities that are otherwise undetected at rest (31). We hypothesise that challenging the maternal CV system with exercise in the pre-conception period may mimic the haemodynamic response to later stages of pregnancy. Previous studies (9, 23, 25, 28, 30, 32) have measured CV parameters at rest, and have not assessed the dynamic function of the system under physiological stress. Moderate, short duration exercise is a safe method of inducing physiological stress and transiently increasing the haemodynamic load without the use of invasive procedures or drugs and will provide an accurate evaluation of global CV function and functional reserve, the latter of which may be indicative of future CV responses during pregnancy.

iii) Recently, it has been shown that LV twist is reduced in high-fitness male volunteers independently of changes in cardiac structure or arterial haemodynamics (14). These findings suggest that changes in LV twist, which have been linked to myocardial efficiency and myofibre stress, may occur prior to other cardiac structural and functional changes such as those associated with the later stages of pregnancy. The assessment of LV twist thus has the potential to be a marker of cardiac (dys)function that may facilitate an earlier risk categorisation of women prior to pregnancy.

IMPORTANCE OF HYPOTHESIS

If PE, in any of its pathogenic isoforms, has preconception origins and CV dysfunction can be detected prior to pregnancy using novel cardiac markers, such as LV twist and by pre-pregnancy response to the physiological stress of exercise, then it will improve understanding of the pathogenesis of the cardiovascular dysfunction in PE. This will allow development of earlier and improved treatment options which may enable reduction in the maternal and perinatal morbidity and mortality.. The intervention and management of risk would require further research. Pre-conception screening, identification of risk factors will provide time to modify these risk factors prior to pregnancy rather than screening at 11-13 weeks of gestation (8). Both techniques employed in this project – echocardiography-derived LV twist and exercise testing – could be implemented into a clinical setting if found to be valuable in identifying high risk women and then targeting preventive strategies for this group.. This hypothesis may identify a tool that is able to predict the future development of PE in pregnancy in a subpopulation of risk patients that may contribute to advancing intervention strategies, such as exercise programmes, and improving management of the disease.

GENERALISABILITY

Typically, large cohorts are studied to determine appropriate diagnostics and interventions in the general population (2, 6). However, large individual variability in the CV adaptation to pregnancy exists. Therefore, the proposed study aims to use a standardised preconception stressor, such as exercise, combined with novel indicators of cardiac stress to potentially identify a woman's individual CV function before pregnancy and relate this to the individual CV adjustments during pregnancy. This individualised approach will hopefully enable to predict CV adaptation to pregnancy on a case-by-case basis and long-term, through a series of careful examinations, provide normal reference values at preconception. Exercise testing and echocardiography may then be included alongside conventional measures in the routine pre-pregnancy evaluation, with the hope to facilitate preventive measures in those women at risk of PE.

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Figure Legend

Figure 1. Hypothetical left ventricular (LV) twist response in three conditions: *Hypothesis 1*) Non-pregnant female at rest and during healthy pregnancy; *Hypothesis 2*) Non-pregnant healthy female at rest and during exercise*; *Hypothesis 3*) Non-pregnant female with future early- or late-onset pre-eclampsia at rest and during exercise. Note the hypothetically higher LV twist at rest and the lower reserve with exercise, similar to that seen with aging (33). *LV twist response of healthy non-pregnant female at rest and during exercise data adapted from Nio *et al.* (27).