PARITY AND CARDIOVASCULAR DISEASE

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A THESIS SUBMITTED TO THE GRADUATE FACULTY OF

WAKE FOREST UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

in Partial Fulfillment of the Requirements

for the Degree of

MASTER OF SCIENCE

Clinical and Population Translational Science

May 2015

Winston-Salem, North Carolina

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Acknowledgements

I would like to thank my mentors, Dr. Herrington, Dr. Solimon and Dr. Rodriguez as well as my thesis committee including Dr. Yeboah and Dr. Beavers who have worked tirelessly to help me develop an understanding of how to perform good research.

I would like to thank my CPTS directors and teachers who have helped me form a basic understanding of research methodologies and my co-authors who have guided me through this process.

Last, but not least, I would like to thank my family, my husband, parents and siblings without whom I would not be here today.
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LIST OF ABBREVIATIONS

BP: Blood Pressure

BSA: Body Surface Area

CAD: Coronary Artery Disease

CHF: Congestive Heart Failure

cIMT: Carotid Intimal-Medial Thickness

CKD: Chronic Kidney Disease

CMR: Cardiac Magnetic Resonance Imaging

CO: Cardiac Output

CVA: Cerebrovascular Accident

DBP: Diastolic Blood Pressure

DM: Diabetes Mellitus

ECM: Extracellular Matrix

EDV: End Diastolic Volume

EF: Ejection Fraction

Hb: Hemoglobin

HDL: High Density Lipoprotein

HFpEF: Heart Failure with preserved Ejection Fraction
HFrEF: Heart Failure with Reduced Ejection Fraction

HR: Heart Rate

HTN: Hypertension

LA: Left Atrium

LMP: Last Menstrual Period

LS: Least squares

LV: Left Ventricle

LVMI: Left Ventricular Mass Index

LVOT: Left Ventricular Outflow Tract

MAP: Mean Arterial Pressure

MESA: Multi-ethnic Study of Atherosclerosis

MI: Myocardial Infarction

MMP: Matrix Metalloproteinase

MRI: Magnetic Resonance Imaging

NHEFS: National Health and Nutrition Examination Survey National Epidemiologic Follow-up Study

PAD: Peripheral Arterial Disease

PV: Plasma volume
SBP: Systolic Blood Pressure

SV: Stroke Volume

TGF: Transforming Growth Factor

TIA: Transient Ischemic Attack

TIMP: Tissue Inhibitor of Metalloproteinase

TNF: Tumor Necrosis Factor

TPVR: Total peripheral vascular resistance

VEGF: Vascular Endothelial Growth Factor
Chapter 1: Physiologic Changes in Pregnancy and the Effects of Parity

INTRODUCTION

In order to support a fetus, the maternal cardiovascular system has to undergo immense adaptations which are generally believed to undergo complete involution (shrinkage/return of an organ to its normal size) after delivery. However, small lines of evidence (detailed later in this chapter) point to a potential pathologic process and differences in outcomes in women with multiple pregnancies which may contradict this common belief that these adaptations normalize post-partum. Studying this may help us understand a more novel risk factor for cardiovascular disease – the process of child-bearing and child-birth or more specifically, parity (technically defined as the number of fetuses a women carries till viability) which is taken as the number of live births. To understand this hypothesis we must first understand the changes which occur in the cardiovascular system during pregnancy and the underlying mechanisms for these changes.

The physiologic adaptations of the cardiovascular system to pregnancy in many ways mimic the pathology of heart failure, while, there are subtle differences which render these changes both healthy and reversible. Here we will review these changes and the current knowledge of the underlying molecular mechanisms. Overall, in normal pregnancy left ventricular (LV) mass, cardiac output and arterial compliance increase and systemic vascular resistance decreases while the effects on diastolic and systolic function are less clear. One caveat is, in a majority of the studies that have determined the physiologic changes in pregnancy, investigators have considered the post-partum structure and function as the baseline for comparison (with the assumption that after involution the cardiac structure and function return to the pre-pregnant state). This, however, does not take into account that there may be incomplete involution of the changes and hence they may be under-estimating the actual change that occurs from a pre-pregnant state. Very few studies have actually enrolled patients prior to pregnancy to obtain baseline data. Furthermore as
many studies enrolled patients late in the 1st trimester much of the early adaptation may also have already occurred prior to enrollment. These are a few of the factors which have led to very variable results between studies, making an accurate analysis of the physiology difficult.

**PHYSIOLOGIC CHANGES IN PREGNANCY**

1. Remodelling of the Heart

1.1 LV Mass and Wall thickness: During pregnancy the myocardium undergoes a reversible “physiologic” hypertrophy with increase in the LV mass by as much as 30-50%.\(^1\)\(^-\)\(^4\) Though there is increase in body mass and body surface area (BSA), the adjusted left ventricular mass index (LVMI) for BSA still increases by variable degrees in different studies from 5-25\% revealing true cardiac hypertrophy in excess of increase in body size.\(^5\)\(^,\)\(^6\) Hypertrophy can be seen as early as 12 weeks while the majority occurs in the third trimester.\(^3\) In the physiologic hypertrophy of pregnancy there is both thickening of myocardium and mild increase in chamber size. Most studies concur that there is none to mild increase in length of the myocyte compared to width (mild eccentric hypertrophy)\(^7\) while in pathologic hypertrophy, the length and breadth increase much more disproportionately: in volume overload models the length increases significantly more than the breadth (eccentric hypertrophy) and vice versa (concentric hypertrophy) in pressure overload models. Studies in pregnant rats have shown that in pregnancy the length to width ratio of myocytes is better preserved.\(^8\) In summary, in physiologic hypertrophy of pregnancy the ratio of LV chamber size to wall thickness (and myocyte length to width ratio) is maintained or mildly increased while in volume overload there is a more drastic increase in this ratio and in pressure overload a decrease in this ratio as shown in figure 1.\(^9\)

1.2 LV Dimensions: The LV end diastolic dimension appears to increase progressively (by about 10\%) till the later part of the second or early part of the third trimester in most studies.\(^10\)\(^-\)\(^12\) However some of these changes were seen only if the patient was examined in the left lateral
position and no significant changes were seen when the measurements were taken with the patients in supine position.\textsuperscript{10} The end systolic dimension changes are less consistent, with some studies showing no change while others show a mild increase at term.\textsuperscript{10-13}

1.3 Atrial Size; The Left atrial (LA) dimension increases by a maximum of 14-16\% reaching the peak size in the third trimester, around 28 weeks and stabilising thereafter.\textsuperscript{10-14} The increases in the LA dimension and end diastolic volume (EDV) are thought to reflect the increase in preload due to the large increase in circulating blood volume as described in the following section.

1.4 LV Outflow tract (LVOT), Aortic Root and Valvular Dimensions; Various studies have measured changes in dimensions at different levels of the LVOT and aorta over the course of pregnancy. The results regarding changes in the LVOT dimensions are variable from no significant change to an increase of 12-16\%.\textsuperscript{3,13,14} However studies which have measured the dimensions of the aortic root have consistently found no significant change.\textsuperscript{10,13-16} The aortic valve area, as well as areas of the pulmonary and mitral valve all increase in size over the gestational period by 14-16\% with significant changes seen at 12 weeks and maximal size attained at 32-38 weeks.\textsuperscript{12}

2. Haemodynamic Changes

Overall in pregnancy the cardiac output, stroke volume, plasma volume and heart rate (HR) increase while the total peripheral vascular resistance (TPVR) and haemoglobin (Hb) decrease with an initial fall in blood pressure (BP) which increases towards term.\textsuperscript{17} The major haemodynamic changes are summarised in figure 2.\textsuperscript{18}

2.1 Heart Rate and Blood Pressure; There is a general agreement amongst all the studies that there is a significant increase in the HR during pregnancy which is partly responsible for the augmentation of cardiac output; however, the degree of increase and gestational timing are
variable in different studies. The HR is significantly increased as early as 5 weeks after the last menstrual period (LMP) and the peak is at around 32 weeks, with the maximal slope of the increase during the 1st and 3rd trimesters. The absolute increase is by 15-27% over baseline values (pre-pregnant or post-partum) and it returns to baseline in 10-14 days. The results from various studies on changes in BP are more variable. While some studies show no significant changes in BP - looking at systolic blood pressure (SBP), diastolic blood pressure (DBP) or mean arterial pressure (MAP) - during the course of pregnancy, the majority show a slight decrease initially with the trough during the second trimester and a slight increase during the third trimester reaching values close to the non-pregnant state.

2.2 Cardiac Output and Stroke Volume: Stroke volume increases by about 20-40% during pregnancy though the timing of increase is very controversial, with some studies revealing an increase during the 1st trimester with even a decline in the 3rd trimester but a larger majority reporting a more gradual increase with peak values during the 3rd trimester. The cardiac output, which was derived from the product of SV and HR in most studies increased by about 50%, some finding HR contributed more and some SV, most of which occurs in the 1st and 2nd trimester. However, one recent study which measured this using cardiac magnetic resonance imaging (CMR) found an increase in cardiac output as high as 80-85%.

2.3 Arterial Compliance and Systemic Vascular resistance: Global arterial compliance, a measure of arterial reservoir-like properties calculated using the diastolic decay of the aortic pressure waveform, increases by about 30% in the first trimester and then remains stable. The total peripheral vascular resistance, calculated from the MAP and cardiac output falls by 40-70% initially, reaching a nadir in the second trimester and then levelling off or slightly increasing in the latter half.
2.4 Blood Volume and Haematologic Changes: During pregnancy, plasma volume increases by 40-50% with a little increase in the first trimester followed by progressive increase to peak volume at 34-36 weeks.\textsuperscript{24, 25} While there is considerable variability with some studies showing a plateau, continued increase or subsequent decline during the latter part of the third trimester, the decline is likely artifactual related to poor mixing of tracer when the woman lies supine and obstructs the circulation to her lower limbs.\textsuperscript{25-27} The increase in red cell mass is comparatively less and peaks earlier (12-28 weeks) leading to the dilutional anemia of pregnancy with a fall in haematocrit evident as early as 7 weeks.\textsuperscript{24, 25, 27, 28} The patterns of change in blood volume reflect those of the plasma volume.\textsuperscript{28}

3. Cardiac Functioning (Systolic and Diastolic)

3.1 Systolic Function: Various studies show inconsistent results on the effects of pregnancy on the systolic function of the heart. The systolic function is generally assessed by ejection phase indices such as ejection fraction or fractional shortening typically obtained by echocardiography. While some studies show an increase in systolic function or no change in the function, several studies also show a small but significant decline in the systolic function.\textsuperscript{3, 9} These changes have however been reported to reverse post-partum. Of note the use of these parameters of systolic function is of limited use as they are significantly dependant on conditions of preload, afterload, mass and heart rate all of which are also significantly altered during pregnancy.

3.2 Diastolic Function: Assessment of diastolic function is a complex process involving assessment of LA dimensions, mitral inflow patterns and pulmonary venous flow patterns as well as, more recently, tissues doppler indices. Results from studies vary based on the methods assessment and also development of methods of assessment over the years. However, those studies which have assessed diastolic function, generally describe a mild impairment during the later stages of pregnancy.\textsuperscript{3, 9}
4. Underlying Mechanisms

The underlying mechanisms of the cardiovascular adaptations of pregnancy are poorly understood. There is little understanding of what induces these changes at a molecular level. Very limited research has been performed looking at gene expression, hormone levels and other molecules to help understand the physiology. Much of this has been in animal models. Following is a brief review of the available literature.

4.1 Hormonal Changes During Pregnancy: After conception human chorionic gonadotropin which rises rapidly initially, peaks at about 10 weeks, then falls to about 30% of the peak, then remaining at a stable level during the remainder of pregnancy falling rapidly to prepregnant levels by 6 weeks post-partum. Progesterone rises gradually throughout pregnancy and falls to prepregnant levels by 6 weeks post-partum. Similarly, estradiol rises throughout pregnancy but it falls rapidly postpartum to levels significantly below pre-pregnant values by 6 weeks post-partum. Relaxin, the first hormone to show a major change rises rapidly with peak values at around 6 weeks and a gradual decline thereafter to less than 50% peak values by 36 weeks and a rapid return to pre-pregnant values by 6 weeks post-partum. These changes are summarized graphically in figure 3.

What exact role these hormones have in the physiologic adaptations is unclear but some have been studied using animal models. Using adult rat myocytes it has been demonstrated that low levels of estrogen produce cardiomyocyte hypertrophy through ERK/NHE-1 activation and intracellular alkalinization whereas an antihypertrophic effect is seen at high concentrations. Also using neonatal rat ventricular myocytes it has been demonstrated that progesterone increased the ventricular myocyte size via phosphorylation of ERK1/2 and inhibition of MEK 1 (upstream from ERK 1/2) effectively blocked progesterone-induced cellular hypertrophy. Hence we see, though the exact role of sex steroid on the physiologic adaptations of the heart to pregnancy is not
clear, they definitely contribute to this process. Another major hormone involved in the physiologic adaptations of pregnancy is relaxin. Through various downstream molecules including endothelins and nitrous oxide, relaxin causes systemic and renal vasodilation and increases vascular compliance, reducing BP as well as increasing renal blood flow and cardiac output. Animal pharmacology data indicate that relaxin, through other downstream molecules such as TNF-α, TGF-β and MMPs has anti-inflammatory and cardiac protective effects, including decrease in fibrosis and inflammation as well as angiogenesis through VEGF. Its biology is summarized in figure 4.4

4.2 Cytokines and Chemokines: In pathologic settings, cytokines and chemokines play an essential role in cardiac remodelling. Rat models have demonstrated that chronic beta-adrenergic stimulation or pressure overload induce myocardial elaboration of pro-inflammatory cytokines and chemokines such as IL-6, IL-1β, TNF-α, TGF-β, NK-κB with associated adverse myocardial remodelling; hypertrophy, fibrosis and dysfunction as well as underlying cellular lesions, necrosis, and apoptosis, increased collagen content and reduced capillary and fibre fractional areas. Furthermore exercise training was demonstrated not only to completely prevent both histo-pathologic changes and remodelling but also prevent pro-inflammatory cytokines and increase anti-inflammatory cytokine IL-10, even in the presence of chronic beta-adrenergic stimulation. In pregnancy the role of cytokines in cardiovascular adaptations is not entirely clear but there appears to be a balance between pro- and anti-inflammatory cytokines including a gradual increase in IL-6, IFN-Υ and GM-CSF, decrease in IL-1α, IL-2 and IL-3 as well as constant levels of IL-4, IL-10 (further increasing during labor), IL-12 and TNF-α which are minimally present in the serum of non-pregnant women. Leukemia Inhibitory factor (LIF), which is known to be important in the establishment of pregnancy is also known to attenuate fibrosis by reducing collagen production. Hence it is likely that this fine-tuning in serum cytokines and chemokines also plays a vital role in cardiovascular adaptations as they are known
to do in both pathologic remodelling and exercise-induced physiologic myocardial hypertrophy with protection from adverse remodelling.

4.3 Extra Cellular Matrix (ECM) Remodelling: An important distinction between physiologic and pathologic hypertrophy is the presence of fibrosis in the interstitium of the pathological myocardium. As we have seen the heart in both exercise and pregnancy related remodelling is protected from fibrosis. The extra-cellular matrix is largely regulated by the matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs). MMPs are a family of structurally related zinc-containing enzymes with proteolytic activity which degrade ECM and connective tissue proteins in the interstitium hence playing an important role in tissue remodelling; while TIMPs are their inhibitory molecules. The matrix metalloproteinase system is not only known to play a vital role in the establishment of pregnancy, such as being partly responsible for the invasive properties of fetal trophoblasts, but also in the maintenance of pregnancy. Further MMPs also play a role in the processes of involution post-partum. Many studies reveal alterations in local levels of MMPs in uterine and placental tissues but some studies have also shown alteration in plasma levels such as higher levels of MMP-2 and MMP-9 in the plasma of pregnant bitches. Animal studies suggest that MMPs are involved in cardiac extracellular matrix remodeling during pregnancy and postpartum. MMP-2 and MMP-3 may be involved in the aortic adaptations in pregnancy. In addition, studies have also shown that MMP and TIMP levels are altered in pressure overloaded hearts, heart failure models and atherosclerosis. There is also evidence that imbalance in the MMPs/TIMPs activity ratio may underlie the pathogenesis of vascular diseases such as abdominal aortic aneurysm, varicose veins, hypertension and preeclampsia. These lines of evidence bring into question whether the effects of these MMPs/TIMPs on the heart during pregnancy may have some long-lasting effects on the extra-cellular matrix.
4.4 Signalling Pathways in Pregnancy Induced Physiologic Cardiac Hypertrophy: The underlying signalling pathways for the physiologic adaptations of pregnancy are not clear. Some studies have looked into the pathways underlying myocardial hypertrophy and there appears to be a cross-talk between both the pathway that underlies the physiologic exercise induced myocardial hypertrophy – PI3K-Akt pathway and those which are stimulated by the pathologic process of pressure overload – the Gαq and MAPK signalling pathways. Pregnancy-induced hypertrophy is mediated by Akt and its downstream molecules, associated with phosphorylation of ERK 1/2 (mediated by progesterone) and requires the activity of calcineurin, which is responsible for the initiation of pathways for physiologic hypertrophy. These pathways are summarized in figure 5 where the red arrows represent the alterations during pregnancy.

EFFECTS OF GRAVIDITY OR PARITY

Gravidity and parity are two terms that refer to the number of times a female has been pregnant (gravidity) and carried the pregnancies to a viable gestational age (parity). In general studies have assessed these parameters as the number of self-reported pregnancies and live births.

1. Effect of Parity on Cardiovascular Adaptations in Pregnancy

In 1997, Clapp et al obtained serial estimates of heart rate, arterial pressure, left ventricular volumes, cardiac output, and calculated peripheral resistance before pregnancy, every 8 weeks during pregnancy, and 12, 24, and 52 weeks postpartum in 15 nulliparous and 15 parous women using electrocardiography, automated manometry, and M-mode ultrasound. They found that heart rate peaked at term and mean arterial pressure reached its nadir at 16 weeks, returning to baseline at term. The increases in left ventricular volumes and cardiac output peaked at 24 weeks as did the decrease in peripheral resistance, and their magnitude was significantly greater in the parous women. Postpartum they gradually returned toward baseline but remained significantly different from pre-pregnancy values in both groups at 1 year. Hence they concluded that cardiovascular
adaptations to the initial pregnancy begin early, persist postpartum, and appear to be enhanced by a subsequent pregnancy.

2. Long term effects of Parity on the Heart

6.1 Effects on Measured Cardiovascular Structure and Function: In 1996 Sadaniantz et al published a small echo based study comparing 20 multiparous women (with 4 or more term pregnancies) to 20 age matched controls. They found no significant differences in chamber dimension, systolic or diastolic function, valvular incompetence, or heart rate between the groups. There was a small, but significant, prolongation in deceleration time of the E wave in the multiparous women. Hence they came to the conclusion that the human heart is generally able to repeatedly adapt to multiple episodes of volume overload in pregnancy without lasting detrimental structural or functional changes. From the Multi-Ethnic Study of Atherosclerosis (MESA) Parikh et al published a paper in 2012 looking at the relationship of the number of live births with cardiac MRI derived LV measures in 2,234 white, black, Hispanic, and Chinese women. They found that with each live birth, LV mass increased 1.26 g; LV end-diastolic volume, 0.74 mL; and LV end-systolic volume, 0.45 mL; LV ejection fraction decreased 0.18% (P trend <0.05). Changes were most notable for the category of women with ≥5 pregnancies. Upon adjustment for potential biologic mediators, live births remained positively associated with LV mass and end-systolic volume. Also from MESA, an abstract was presented in the AHA 2012 sessions wherein the investigators found that in 3322 women ever-pregnant women had lower carotid artery distensibility compared to never pregnant women.

6.2 Effects on subclinical markers of CVD: In 2010 investigators from Cardiovascular Risk in Young Finns study looked at 3596 participants who were recruited during childhood/adolescence and had 21 and 27 year follow ups done at which time carotid intimal medial thickness (cIMT), carotid elasticity and brachial flow mediated dilation were used to assess sub-clinical
atherosclerosis. Complete data was available in 1786 pts. In the 6 years between the 2 follow up
visits participants who had been pregnant showed increased progression of cIMT. This
association slightly weakened (p from 0.02 to 0.05) by adjusting for concurrent changes in CV
risk factors (decreased HDL, apo a-1, apo b and redistribution of adiposity to abdominal
distribution) however the number of births was directly associated with progression.53

6.3 Effects on hard clinical outcomes: In 1993 Ness et al published a study with combined data
from Framingham Heart Study and the first National Health and Nutrition Examination Survey
National Epidemiologic Follow-up Study (NHEFS) looking at post-menopausal white women to
assess if there was any association between gravidity and cardiovascular events including
coronary artery disease (CAD), cerebrovascular accident (CVA) and congestive heart failure
(CHF).54 One group comprising 2357 women were followed for 28 years and the other
comprising 2533 women was followed for at least 12 years. The results revealed that a gravidity
of 6 or more was associated with a small but consistent increased risk of coronary and
cardiovascular disease [which includes coronary disease (angina, myocardial infarction (MI),
coronary or sudden death), CVA/transient ischemic attack (TIA), intermittent claudication,
CHF].54 However in 1987 some results from the Nurses’ Health Study had been published where
investigators had followed 119,963 women in the United States aged 30-55 for 6 yrs for
Myocardial infarction or fatal coronary disease. During 700,809 person-years of observation, 308
incident cases of nonfatal myocardial infarction or fatal coronary heart disease occurred but this
study revealed no difference between nulliparous and multiparous women in their risk for CAD.55

CLINICAL EQUIPOISE AND OUR CONCEPTUAL MODEL

From the above review it is clear that there are significant changes that occur in the
cardiovascular system during pregnancy and that there is significant equipoise regarding whether
or not complete involution takes place. A further hypothesis is that multiple pregnancies,
especially if occurring in close succession, may lead to some lasting effects on the cardiovascular system which may explain some of the findings of worse outcomes in women with a high gravidity/parity level. This also brings up the possibility that parity may in some part be responsible for some gender differences in cardiovascular disease.

Based on the available literature we propose the conceptual model shown in figure 6. We propose that the multiple cycles of the physiologic changes of pregnancy induced by various mechanisms such as release of relaxin, nitrous oxide and alterations in MMPs and TIMPs may lead to some extracellular matrix remodelling: alteration of collagen, apoptosis, replacement fibrosis, hypertrophy, lipid and calcium deposition. This process would be complicated by many different risk factors for cardiovascular disease including demographic parameters such as age, race/ethnicity; biologic parameters such as height, weight, hypertension (HTN), diabetes mellitus (DM), cholesterol, chronic kidney disease (CKD), obesity; life-style measures such as smoking, alcohol consumption, physical activity as well as different socio-economic and environmental factors. Some of these such as HTN and adiposity redistribution may also be mediating factors. Ultimately these tissue level changes may manifest as subclinical cardiovascular disease including increased arterial and LV stiffness, hypertrophy, loss of contractile function and diastolic dysfunction as well as atherosclerotic plaque formation, inflammation and obstructive processes. Ultimately this may manifest as clinical cardiovascular disease such as aortic aneurysms, heart failure with preserved ejection fraction (HFP EF), heart failure with reduced ejection fraction (HFR EF), CAD and peripheral arterial disease (PAD).
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Figure 1. Morphometric Alterations in Response to Various Stimuli – Physiologic and Pathologic Hypertrophy⁹
Figure 2. Haemodynamic Changes During Pregnancy\textsuperscript{18}

Figure 3. Hormonal Changes During Pregnancy by Gestational Age\textsuperscript{30}
Figure 4. Biology of Effects of Relaxin During Gestation\textsuperscript{34}
Figure 5: Signalling Pathways for the Physiologic Hypertrophy During Pregnancy
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Chapter 2: Parity is associated with Aortic Stiffness, Remodelling and All-cause Mortality:

The Multi-ethnic Study of Atherosclerosis (MESA)

ABSTRACT

Introduction: Several lines of evidence suggest that increased gravidity and/or parity is associated with increased risk for clinical cardiovascular events although there are no data on the effects on central aortic stiffness or remodelling. We examined the relationship between live births and central aortic pressure indices, magnetic resonance imaging (MRI)-based measures of aortic dimensions, congestive heart failure (CHF), cardiovascular events (CVE) and all-cause mortality in women enrolled in the Multiethnic Study of Atherosclerosis (MESA).

Methods: Study subjects included 3592 women aged 45-84 years, classified as having 0, 1, 2, 3, 4, or ≥5 live births. Women had arterial tonometry (n=1908) to assess central pressure indices and a standardized MRI exam (n=3221) to assess aortic dimensions. Events were adjudicated over 10 years in 3592 women. Univariate/multivariable regression models, Kaplan Meier and Cox proportional hazard models were used to assess the relation between parity and various outcomes.

Results: Of 3592 women, 13.7% were grand multiparous (≥5 live births), mean age was 62.1 (±10.3) years, 41% had been smokers, 11% had diabetes mellitus and 39% were on anti-hypertensive medications. Pulse pressure amplification (PPA) was 0.4% lower (SE 0.09%) and reflection magnitude (RM) was 0.1% higher (SE 0.05%) for each live birth (all p<0.01) and remained significant (all p≤0.05) on multivariable adjustment. Aortic area was 14 mm² larger and average diameter was 0.29 mm greater for each live birth (p<0.001) which remained significant on adjustment (p<0.005). In adjusted Cox proportional hazard models, parity was significantly associated with all-cause mortality (p<0.03).
Conclusions: Greater numbers of live births may be associated with greater arterial stiffness, aortic remodelling and an increased risk of all-cause mortality.

Key Words: parity, central pressure indices, arterial stiffness, aortic dimensions, aortic remodelling, heart failure, cardiovascular disease, death
Background

Cardiovascular disease pathology differs considerably between women and men. While hypertension (HTN) tends to develop earlier in men, it is more poorly controlled in women.\(^1\) Not only is female gender a risk factor for isolated systolic HTN but by the sixth decade the prevalence of benign HTN in women exceeds that in men.\(^2,3\) While male gender is a traditional risk factor for coronary artery disease (CAD), women tend to have more microvascular pathology and worse outcomes.\(^4,5\)

Amongst several intrinsic differences between the genders, one prominent difference is in the exposure of women to childbearing and childrearing. In the 1990s it was noted that women with 6 or more pregnancies had a small but consistently increased risk for both coronary and all cardiovascular disease compared to nulliparous women (women with no prior live births).\(^6\) Also parous women have a higher mortality from diabetes mellitus (DM), HTN, CAD, cerebrovascular disease.\(^7\) However, the mechanism(s) that account for these associations remain unclear. Recent analyses from MESA indicate that parity is also associated with increased carotid stiffness as well as some left ventricular (LV) remodelling.\(^8,9\)

While it is evident that there is significant change in arterial compliance during pregnancy, long-term vascular effects have not been studies. To date there are few data on the effects of gravidity or parity on central aortic structure and function. Indices of central aortic pressure, measured by arterial tonometry, have emerged as a novel non-invasive method of assessing aortic and arterial stiffness. These indices are calculated from the aortic wave profile which is formed by the interaction between the central aortic pressure and a reflected waveform from the peripheral arterial tree which returns to the proximal aorta in mid-late systole causing a second peak in the pressure waveform.\(^10\) The waveform is derived by the application of a transfer function to the radial waveform and hence measured non-invasively.\(^11,12\) From this waveform the pulse pressure
amplification (PPA), Augmentation Index (AIx) and reflection magnitude (RM) are calculated. While RM and AIx are directly related to aortic/arterial stiffness, PPA is inversely related. Measures of central pressure not only predict major adverse cardiac outcomes and death but are also more strongly related to cardiovascular disease than brachial blood pressure.\textsuperscript{14, 15}

Another measure of aortic remodelling is aortic dimensions. A recent study revealed that the ascending aortic diameter indexed to body surface area (BSA) was independently associated with a composite of cardiovascular disease (CVD) and mortality.\textsuperscript{16} Extreme aortic remodelling results in the formation of aneurysms in which there is cystic medial degeneration appearing histologically as smooth muscle cell dropout and elastic fiber degeneration causing weakening of the muscle wall and a propensity for rupture.\textsuperscript{17} Cardiac MRI is considered a gold standard for measurement of aortic dimensions.

A. We hypothesised that extra-cellular matrix remodelling that occurs to facilitate child birth may also lead to adverse effects on LV and arterial structure and function. To assess these effects we proposed the following aims: To study the effects of parity on central aortic structure and function by examining the relationship between reproductive history and central aortic pressure indices (in lieu of aortic stiffness) as well as MRI-based measures of aortic dimensions in women enrolled MESA.

B. To study the association of parity with clinical congestive heart failure (CHF), cardiovascular events (CVE) and all-cause mortality as adjudicated in MESA over a 10 year follow-up period.

Methods

Study Population
The MESA is a multicenter, multi-ethnic, prospective cohort study of individuals aged 45-84 years, who were free of clinical cardiovascular disease at baseline (2000-2002), from 6 US communities - Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN. The details of recruitment have been previously described. The cohort consisted of participants from diverse racial/ethnic backgrounds including Caucasians, Chinese-Americans, African-Americans, and Hispanic-Americans. The study was approved by the institutional review boards of all participating centers, and participants gave written informed consent.

Assessment of Parity as an Independent Variable

Parity was defined as the self-reported number of live births, assessed during the baseline exam. Questions asked were whether the participant had ever been pregnant, number of pregnancies and number of live births. Five women were excluded for incomplete responses. Thirty-six women had the number of reported live births exceeding the number of pregnancies and in these individuals parity was assumed to be the number of pregnancies rather that the number of live births, presuming that this difference was because of multiple births as has been done in previous studies.

Parity was tested both as a continuous variable and a categorical variable to assess for a non-linear relationship. Those with more than 5 live births were considered as a parity of 5. For Kaplan-Meier and Cox proportional hazard models, parity was further collapsed into categories of 0, 1-4 live births or ≥5 live births (grand-multiparous).

Assessment of Covariates

Standard questionnaires were administered for the determination of some covariates while others were measured. Age, race/ethnicity, educational attainment, current antihypertensive medication
use and smoking were self-reported. Smoking was defined as the use of >100 cigarettes during the participants’ lifetime. Height and weight were measured. Blood pressure was measured as the average of the second and third readings taken using Dinamap automated blood pressure device (Dinamap Monitor Pro 100) using appropriate Critikon cuff sizes as per the Critikon sizing chart. Total cholesterol and high-density lipoprotein were obtained from fasting lipid profiles. Diabetes mellitus was defined as fasting blood glucose ≥7 mmol/L or antidiabetic medication use.

Central Pressure Outcome Measurements by Arterial Tonometry

Radial arterial waveforms were obtained with the participants in supine position using HDI/PulseWave-CR2000 tonometry device (Hypertension Diagnostics, Eagan, Minnesota), digitized at 200 Hz and exported for offline processing using custom-designed software written in Matlab (The Mathworks, Natick, Massachusetts) as previously described. From this waveform the central aortic pressure waveform was obtained using a generalized transfer function. From the central aortic pressure waveform 3 indices were derived: PPA, AIx and RM. PPA was calculated by multiplying the ratio of the radial pulse pressure to the aortic pulse pressure by 100. After identifying the first and second peaks in the central aortic pressure waveform, AIx was calculated by multiplying the ratio of the second to the first systolic peak by 100. After further separating the central aortic pressure waveform into the forward and backward waves, RM was calculated by multiplying the ratio of the backward wave amplitude to the forward wave amplitude by 100.

Aortic Dimensions by Cardiac MRI

Cardiac MRI was performed using 1.5-T whole-body MRI systems: Signa CV/i or Signa LX (GE Medical Systems, Waukesha, Wisconsin). MRI of the aorta was performed using a double inversion-recovery black-blood fast spin-echo sequence with electrocardiographic gating. Axial images of the ascending thoracic aorta were obtained at the level of the right pulmonary artery at
mid-diastole. Imaging parameters were as follows: repetition time = 2 RR intervals; echo time = 42 msec; field of view = 36 cm; slice thickness = 6 mm; matrix size = 512 × 256, interpolated to 512 × 512; echo train length = 32; and receiver bandwidth = 62.5 kHz.¹⁹

**Ascertainment of Clinical Outcomes**

While parity was assessed at the baseline exam (2000-2002), clinical events were adjudicated using standard criteria over 10 years until MESA exam 5 (2010-2012), by a committee that included a cardiologist, a cardiovascular physician-epidemiologist, and a neurologist. Incident CHF, definite or probable, required heart failure symptoms such as shortness of breath or edema; probable CHF required CHF diagnosed by a physician and the patient receiving medical treatment for CHF while definite CHF required other criteria, such as pulmonary edema/congestion by chest x-ray; dilated ventricle or poor LV function by echocardiography or ventriculography or echocardiographic evidence of LV diastolic dysfunction. Participants who had only a physician diagnosis of CHF without any other evidence were classified as absent CHF. Individuals with adjudicated definite or probable CHF were used in our analysis. An incident CVE was defined as a composite of adjudicated myocardial infarction (MI), stroke, resuscitated cardiac arrest, angina if followed by percutaneous coronary intervention or coronary bypass grafting, and CVD death. A composite of CVE and CHF, referred to as CVE/CHF, was also used in our analysis as was all-cause mortality.

**Statistical Analysis**

The sample size differed for the 3 different outcome categories. Of total 3592 women included in the study, complete data on central pressure indices was available for 3221 of these participants, complete MRI data was available on 1908 and complete data on clinical outcomes was available for the entire cohort. Descriptive summary statistics were generated (in the complete cohort) overall and by 6-level parity for the analytic sample. Means and standard deviations were
reported for continuous variables and relative frequencies for categorical variables. Bivariate associations between baseline characteristics and parity were assessed using ANOVA and chi square tests. Nested multivariable linear regression models assessed the relationship between parity, treated as a continuous as well as categorical variable (to assess for a non-linear relationship) and continuous outcomes of interest (parameters of central pressure derived from central pressure waveforms, minimal and maximal aortic areas, and average aortic diameter). For clinical outcomes (incident CHF, CVE and all-cause mortality) Kaplan Meier plots and Cox proportional hazards models were generated. The multivariable models were adjusted for covariates as follows:

Model 1: Age, race/ethnicity

Model 2: Height, weight, smoking, diabetes, total and HDL cholesterol, SBP and use of anti-hypertensive medications use in addition to variables in model 1

Model 3: Highest level of education completed as a proxy for socio-economic status in addition to variables in model 2

Beta estimates and standard errors were reported for linear models. Line graphs were used to visually represent the least square means of the unadjusted models by increasing levels of parity. A p-value of < 0.05 was considered statistically significant and all analyses were performed using JMP®Pro 11.0.0.

Results

Subjects

Of 3592 women, 18.0% were nulliparous (no live births) and 13.7% were grand multiparous (≥5 live births). The mean age was 62.1 (±10.3) years, 40.8% had smoked more than 100 cigarettes in their lifetime, 11.4% had diabetes mellitus (treated or untreated) and 38.5% were on anti-
hypertensive medications. Baseline characteristics by parity are detailed in table I. Women with higher parity were older, shorter, had lower HDL, higher SBP (and more on anti-hypertensives), smoking and diabetes. Hispanics tended to have higher parity and Caucasians lower. Level of education was also inversely related to parity.

Central Pressures

Complete data on central aortic pressures, after data cleaning, was available on 3221 participants. In univariate analyses, PPA was 0.4% lower (SE 0.09%, p<0.01) and RM was 0.1% higher (SE 0.05%, p<0.01) for each live birth. AIx was not significantly related to parity, likely due to significant variability and large standard errors. Least squares (LS) means for models in which parity was classified as categorical are shown in figure 1. In multivariable models adjusted for age, race-ethnicity, height, weight, smoking, diabetes, total and HDL cholesterol, SBP and use of anti-hypertensive medications PPA was 0.3% lower (SE 0.09%, p<0.01) and RM was 0.1% higher (SE 0.06, p=0.05). On further adjustment for education, as a proxy for socio-economic status (SES), the association of parity with RM was no longer statistically significant. Details of the unadjusted and nested multivariable linear regression models are shown in table II.

Aortic Dimensions

Analysis of association of parity with aortic dimensions was done in the 1908 women with complete MRI data available. In univariate analyses, minimum and maximum aortic area were 14 mm² larger (SE 2.4, p<0.001) and average diameter was 0.29 mm greater (SE 0.05, p<0.001) for each live birth. LS means for models in which parity was classified as categorical are shown in figure 1. In multivariable models adjusted for race-ethnicity, height, weight, smoking, diabetes, total and HDL cholesterol, SBP and use of anti-hypertensive medications the minimum aortic area was 7.5 mm² larger (SE 2.3, p=0.001), maximum aortic area was 8.3 mm² larger (SE 2.4, p<0.001) and average diameter was 0.16 mm greater (SE 0.05, p<0.001) for each live birth. This
relationship did not change with further adjustment for education as a proxy for SES. Details of the unadjusted and nested multivariable linear regression models are shown in table III.

**Clinical Outcomes**

A total of 3592 women had complete data available for reproductive history as well as clinical events on follow-up. Overall, the participants were followed for an average of 9.9 (±1.7) years. Over a median follow-up of 10.4 years (Interquartile range 9.8-10.8) there were 98 cases of CHF, 256 cases of CVEs, 305 participants developed CVE/CHF and 301 participants died. The frequency of events by 3-level parity is shown in figure 2.

In Kaplan-Meier analysis, using 3-level parity as the exposure, there was a significantly higher risk of all-cause mortality in grand-multiparous women compared to those with a lower number of live births and also a trend towards higher CVE and CHF/CVE but not CHF alone as shown in figure 3. Interestingly, the category of women with 1-4 live births showed lower all-cause mortality than nulliparous women. Further pair-wise analysis comparing women with 1-4 live births to grand-multiparous women (as these categories showed the greatest separation in the initial Kaplan-Meier analysis) revealed a stronger association of parity with CVE and CVE/CHF which did reach statistical significance as shown in figure 4. In fully adjusted Cox proportional hazard models (Model C), the association of parity with all-cause mortality still remained significant (overall p<0.03) while all other associations lost significance as shown in table IV.

**Discussion**

**Summary of Findings compared with prior literature**

Among 3592 women of multi-ethnic origins, parity was associated with detrimental central pressure indices suggestive of arterial stiffening and increasing aortic dimensions. To our knowledge this is the first study which has examined this association. We also noted a trend
towards increased number of CVEs and a statistically significant association of parity with all-cause mortality. The relationship with all-cause mortality was non-linear; parity with lower number of live births (1-4) appeared to be at the lowest risk for mortality with a significantly increased risk if the number of live births was 5 or more. This is in agreement with prior literature which shows a small but significantly higher rate of CVD in women with 6 or more pregnancies as well as an increased mortality in women with high parity. Like prior studies our data also reveals that nulliparous women have a higher mortality than women with low parity which prior studies have shown was explained by an increase in accidental deaths in this category.

Though our study did not show a significant association of parity with CHF, we were likely underpowered to show this as there were a limited number of events.

Underlying Mechanisms and Conceptual Model

During pregnancy it is clear that the cardiovascular system undergoes immense adaptations in order to support the growth of the fetus. The LV remodels, undergoing a physiologic form of hypertrophy with alteration in its systolic and diastolic function and extensive hemodynamic changes. Global arterial compliance increases by about 30% and the total peripheral vascular resistance falls by 40-70%. The mechanisms underlying these adaptations are poorly understood. It is clear that the hormone, Relaxin, plays a vital role in vasodilation and angiogenesis as well as protecting the LV from fibrosis and inflammation during its hypertrophy through downstream effects of nitrous oxide, vascular endothelial growth factor (VEGF), endothelins, matrix metalloproteinases (MMPs), tumor necrosis factor (TNF)-α and transforming growth factor (TGF)-β. A delicate balance needs to be maintained between extracellular matrix (ECM) regulatory molecules, MMPs and tissue inhibitor of metalloproteinases (TIMPs), to both facilitate relaxation of tissues for the process of childbirth and protect the ECM of the heart from fibrosis during these adaptations. However, little is known of the long-term effects of these changes occurring repeatedly.
We hypothesise that these adaptations, when occurring repeatedly, possibly with incomplete involution may have long-lasting effects on the cardiovascular system including extracellular matrix remodelling, alteration of collagen, apoptosis, replacement fibrosis, hypertrophy, lipid and calcium deposition. This process would be complicated by many different risk factors for cardiovascular disease including demographic parameters such as age, race/ethnicity; biologic parameters such as height, weight, HTN, DM, cholesterol, chronic kidney disease (CKD), obesity; life-style measures such as smoking, alcohol consumption, physical activity as well as different socio-economic and environmental factors. Some of these such as HTN and adiposity redistribution may also be mediating factors. Ultimately these tissue level changes may manifest as subclinical cardiovascular disease including increased arterial and LV stiffness, hypertrophy, loss of contractile function and diastolic dysfunction as well as atherosclerotic plaque formation, inflammation and obstructive processes. Finally these would manifest as clinical cardiovascular disease such as aortic aneurysms, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), CAD and peripheral arterial disease (PAD). This conceptual model is illustrated in figure 5.

**Strengths and Limitations**

Our study demonstrates the possibility of a new novel risk factor for CVD – high parity. To our knowledge, ours is the first study to evaluate the association of parity with aortic dimensions and stiffening. In this manner our study is helping facilitate the understanding of the mechanisms by which this novel risk factor could be responsible for an increased risk of CVD amongst women. Our study also has the benefit of an ethnically diverse population.

One concern is that we have not taken into account the time interval between pregnancies which could potentially have a significant effect on the associations observed. However, this is a very difficult predictor to evaluate, especially since the intervals even within a subject may vary
considerably. Furthermore, we did not have information on the intervals between subsequent pregnancies though some of this would be partially accounted for by age and the total number of pregnancies. Potential confounders such as pre-eclampsia, gestational diabetes and gestational HTN have also not been adjusted for but some of these may be accounted for by the presence of pre-diabetes or higher SBP which were included as covariates. Another consideration for future studies is the psychosocial effects of child-rearing which could be evaluated by assessing for any such associations in men based on their number of children.

Conclusions

Higher parity is associated with increasing arterial stiffness and aortic remodelling. A high level of parity, specifically five or more live births, is also possibly a risk factor for CVD in general and all-cause mortality. Further studies are needed to determine if parity is associated with CHF and to understand the underlying pathophysiology for this apparent deleterious consequence on arterial structures and cardiovascular outcomes. If parity is truly a novel risk factor for CVD, the underlying mechanisms need to be studied to determine if there are any potential preventive strategies.
References


27. Chung E, Leinwand LA. Pregnancy as a cardiac stress model. *Cardiovascular research.* 2014

Table I: Baseline Characteristics (Relative Frequency or Mean (SD))

<table>
<thead>
<tr>
<th>Parity</th>
<th>Overall N=3592</th>
<th>0 Births N=645 (18.0%)</th>
<th>1 Birth N=532 (14.8%)</th>
<th>2 Births N=873 (24.3%)</th>
<th>3 Births N=675 (18.8%)</th>
<th>4 Births N=376 (10.5%)</th>
<th>5+ Births N=491 (13.7%)</th>
<th>p-value</th>
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</thead>
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<td><strong>Age (years)</strong></td>
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<td></td>
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<td>&lt;0.01</td>
</tr>
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<td>Overall</td>
<td>62.1 (10.3)</td>
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<td>60.1 (10.1)</td>
<td>60.6 (9.8)</td>
<td>62.3 (9.6)</td>
<td>64.3 (10.1)</td>
<td>67.6 (8.7)</td>
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<td>Overall</td>
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<td>Overall</td>
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<td>165.0 (40.6)</td>
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<td>163.0 (37.5)</td>
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<td>Impaired Fasting Glucose</td>
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<td>11.0</td>
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<tr>
<td><strong>SBP (mmHg)</strong></td>
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<td></td>
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<tr>
<td>Overall</td>
<td>127.1 (23.2)</td>
<td>124.5 (22.8)</td>
<td>125.1 (22.9)</td>
<td>125.3 (22.7)</td>
<td>127.2 (22.5)</td>
<td>129.4 (23.9)</td>
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<td>Anti-HTN meds</td>
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<td><strong>Tot Chol (mg/dL)</strong></td>
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<td>Overall</td>
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<td>199.3 (34.3)</td>
<td>197.2 (35.6)</td>
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<td>HDL (mg/dL)</td>
<td>56.3 (15.3)</td>
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<td>Graduate or professional school</td>
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39
Table II: Association of central pressure indices with number of live births

<table>
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<tr>
<th></th>
<th>Pulse Pressure Amplification</th>
<th>Augmentation Index</th>
<th>Reflection Magnitude</th>
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<tr>
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<td>Estimate (SE) p-value</td>
<td>Estimate (SE) p-value</td>
<td>Estimate (SE) p-value</td>
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<tr>
<td>Univariate</td>
<td>-0.38 (0.09) &lt;0.001</td>
<td>0.20 (0.26) 0.46</td>
<td>0.14 (0.05) &lt;0.01</td>
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<tr>
<td>Model A*</td>
<td>-0.20 (0.09) &lt;0.05</td>
<td>0.03 (0.28) 0.91</td>
<td>0.11 (0.06) 0.05</td>
</tr>
<tr>
<td>Model B**</td>
<td>-0.27 (0.09) &lt;0.01</td>
<td>0.17 (0.27) 0.53</td>
<td>0.11 (0.06) 0.05</td>
</tr>
<tr>
<td>Model C***</td>
<td>-0.27 (0.10) &lt;0.01</td>
<td>0.15 (0.28) 0.59</td>
<td>0.10 (0.06) 0.09</td>
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</tbody>
</table>

* age, race/ethnicity adjusted

** Model A + biologic variable adjusted (height, weight, smoking, diabetes, total and HDL cholesterol, SBP, htn med)

*** Model B + education adjusted as proxy for SES

Table III: Association of aortic dimensions with number of live births

<table>
<thead>
<tr>
<th></th>
<th>Minimum Aortic Area (mm²)</th>
<th>Maximum Aortic Area (mm²)</th>
<th>Average Aortic Diameter (mm)</th>
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<tbody>
<tr>
<td></td>
<td>Estimate (SE) p-value</td>
<td>Estimate (SE) p-value</td>
<td>Estimate (SE) p-value</td>
</tr>
<tr>
<td>Univariate</td>
<td>14.13 (2.4) &lt;0.001</td>
<td>14.31 (2.4) &lt;0.001</td>
<td>0.29 (0.05) &lt;0.001</td>
</tr>
<tr>
<td>Model A*</td>
<td>8.40 (2.4) &lt;0.001</td>
<td>9.62 (2.5) &lt;0.001</td>
<td>0.18 (0.05) &lt;0.001</td>
</tr>
<tr>
<td>Model B**</td>
<td>7.52 (2.3) &lt;0.01</td>
<td>8.34 (2.4) &lt;0.001</td>
<td>0.16 (0.05) &lt;0.001</td>
</tr>
<tr>
<td>Model C***</td>
<td>7.04 (2.4) &lt;0.01</td>
<td>7.90 (2.5) &lt;0.01</td>
<td>0.15 (0.05) &lt;0.01</td>
</tr>
</tbody>
</table>

* age, race/ethnicity adjusted

** Model A + biologic variable adjusted (height, weight, smoking, diabetes, total and HDL cholesterol, SBP, htn med)

*** Model B + education adjusted as proxy for SES
Table IV: Association of Parity with Clinical Outcomes (Fully-adjusted Cox proportional hazard models for age, race/ethnicity, height, weight, smoking, diabetes, total and HDL cholesterol, SBP, htn med, education)

<table>
<thead>
<tr>
<th></th>
<th>At risk</th>
<th>Events (%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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</thead>
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<tr>
<td></td>
<td>Nulliparous**</td>
<td>1-4 Live Births</td>
<td>Grand-multiparous**</td>
<td>Nulliparous</td>
</tr>
<tr>
<td>CHF*</td>
<td>645</td>
<td>2456</td>
<td>491</td>
<td>18 (2.8)</td>
</tr>
<tr>
<td>CVE*</td>
<td>645</td>
<td>2456</td>
<td>491</td>
<td>44 (6.8)</td>
</tr>
<tr>
<td>CVE/CHF*</td>
<td>645</td>
<td>2456</td>
<td>491</td>
<td>55 (8.5)</td>
</tr>
<tr>
<td>Death</td>
<td>645</td>
<td>2456</td>
<td>491</td>
<td>62 (9.6)</td>
</tr>
</tbody>
</table>

*CHF: congestive heart failure; CVE: cardiovascular events; CVE/CHF: Composite of cardiovascular events and CHF

**Nulliparous: No live births, Grand-multiparous: ≥5 live births
Figure 1: Univariate association of Parity as a categorical variable with Central Pressure Indices and Aortic Dimensions
Figure 2: Frequency of Clinical Events by Parity over median 10 year follow-up period
Figure 3: Kaplan-Meier Curves for Clinical Outcomes by 3-level Parity
Figure 4: Kaplan-Meier Curves for Clinical Outcomes comparing women with 1-4 live births to grand-multiparous women
Figure 5: Conceptual Model
Chapter 3: Further Study Using the Echocardiographic Study of Latinos (Echo-SOL) database

Is there an Association Between Parity and LV Remodelling and LV Stiffness?

Our work in the MESA cohort suggests that high parity may be associated with aortic remodelling and increased aortic or arterial stiffness; however, there is not much data exploring a possible association between parity and LV remodelling or LV stiffness. LV stiffening and impaired relaxation are thought to be responsible for heart failure with preserved ejection fraction (HFP EF). HFP EF is becoming a growing public health problem with recent data revealing, that while its prevalence is increasing, its death rate remains unchanged.1 Across multiple epidemiologic studies women have been noted to be at a significantly higher risk for HFP EF than men without any clear explanation to why such a disparity exists.2–5 We hypothesize that the process of child-bearing and child-birth, which is exclusive to women, may contribute to this female predominance.

A German echocardiographic study of the structural effects of pregnancy on the heart in the peripartum period has shown that diastolic dysfunction and left ventricular hypertrophy (LVH) persisted for 2 months while systolic function normalized within a week.6 A study comparing the structural changes in primiparous and multiparous women both during pregnancy and 1 year post-delivery showed that the cardiovascular adaptations to the initial pregnancy begin early, persist postpartum, and appear to be enhanced by subsequent pregnancies without complete involution even 1 year after delivery.7 In the multi-ethnic study of atherosclerosis (MESA), it has been shown that there is a positive association between parity and left ventricular (LV) mass, LV end systolic volume and a negative association between parity and LV ejection fraction (EF) and these associations persist despite adjustment for systolic blood pressure, anti-hypertensive
medications, lipids (total cholesterol/ high density lipoprotein (HDL)/ triglycerides), diabetes mellitus (DM) and body mass index (BMI).8

Hispanic/Latina Population and Parity

Amongst different racial/ethnic groups, higher parity has been observed amongst Hispanic/Latina population.9 Previous literature from as early as the 1990s indicates that having six or more pregnancies is associated with an increased risk of cardiovascular disease and there may be even a trend towards heart failure10. However, this relationship has not been studied in Hispanic/Latina population despite the higher parity observed in this ethnic group. To examine the relationship between parity and various echocardiographic parameters including cardiac volumes, mass, ejection fraction, stroke volume, LVH and diastolic dysfunction in a population-based cohort we have started performing a similar analysis in the Echocardiographic Study of Latinos (Echo-SOL) cohort, a community based cohort of self-identified Hispanic/Latino women. Methods and preliminary results will be included here.

Hypothesis

We hypothesized that higher parity would be associated with higher cardiac volumes, mass, systolic and diastolic dysfunction.

Methods

The Hispanic Community Health Study (HCHS)/Study of Latinos (SOL) is a community based cohort study of self-identified Hispanic/Latino persons from randomly selected households in four U.S. field centers (Chicago, IL; Miami, FL; Bronx, NY; San Diego, CA). The baseline examination was conducted from 2008 to 2011. The sample design and cohort selection has been previously described11. The Echo-SOL, an ancillary study to the HCHS/SOL was designed to provide echocardiographic parameters characterizing cardiac structure and function in a
representative HCHS/SOL baseline subsample of participants 45 years and older. Echo-SOL used a stratified random sampling design to assure that Echo-SOL represents not only the overall HCHS/SOL population but also the Hispanic subgroup distribution found in HCHS/SOL. A detailed description of the design, rational and methods has been described elsewhere (in press).12

Across all Echo-SOL sites, participation rates averaged ~80%, and participant enrollment was conducted from October 2011 through June 2014.

Participants included 1172 Hispanic/Latina women, aged 45 and older, who were enrolled in Echo-SOL, representative of several Hispanic backgrounds. Data acquisition was performed using a standard protocol developed by the principal investigator, study sonographer and study coordinator after pilot testing at Wake Forest School of Medicine (WFSM). Echocardiogram studies were sent electronically through a fully encrypted, regulatory compliant secure server to WFSM Echo-SOL reading center along with a data tracking form. Reproductive history was obtained by questionnaire in the baseline HCHS/SOL exam.

**Independent Measures**

Parity was defined two ways as an ordinal categorical variable: 1) 6-level variable with categories 0-4 and a 6th category including women with five or more live births; 2) Collapsed categories with 0, 1-4 and ≥5 live births. The first definition was used in linear regression and the later in logistic regression modeling.

Demographic, behavioral, clinical, and psychosocial variables included age, body mass index (BMI), education, income, smoking status, systolic blood pressure (SBP), diabetes, use of anti-hypertension medications, total and high-density lipoprotein (HDL) cholesterol. Education was categorized as < high school, high school or equivalent, and > high school and income was classified as <$20,000, $20,000-$40,000, and >$40,000. Diabetes was categorized as non-diabetic, pre-diabetic, and diabetic. Smoking status (current vs. former/non-smokers) and use of
anti-HTN medications were considered nominal variables. SBP and both cholesterol measures were included as continuous variables.

**Echocardiographic Outcome Measurements**

To maintain consistency across sites only one ultrasound imaging platform was used: Philips Ultrasound IE-33 or Sonos 5500/7500 with software Version D.2 or higher. This equipment is interfaced with a standard 2.5- to 3.5-MHz phased-array probe, according to the recommendations of the American Society of Echocardiography (ASE). Standard echocardiographic examination, including M-mode, two-dimensional (2D), spectral, color flow and tissue Doppler study, was performed by experienced sonographers at each Field Imaging Center\(^ {13}\). With the subjects in partial left decubitus position and breathing normally, images were obtained, together with a simultaneous ECG signal, along the parasternal long and short axes and from the apical 4- and 2-chamber long-axis views\(^ {14}\).

2D echocardiography was used to image the Left ventricle (LV) in the parasternal long axis view and to locate the M-mode cursor just below the mitral leaflet tips. LV chamber size and wall thickness were assessed by multiple linear dimensions that were measured from the parasternal long axis view. 2D guided M-mode methods were used for determining LV mass (LVM) as have been well validated in autopsy studies.\(^ {15,16}\) 2D imaging of the LV was performed from the parasternal long axis, parasternal short axis (basal, mid and apical), apical four-chamber, apical two-chamber, and apical long-axis views to obtain in the best possible 2D images of the LV endocardium without foreshortening of the LV cavity or echo ‘drop out’ in order to measure LV volumes and ejection fraction.

Doppler recording of transmirtal inflow velocities (mitral E and A waves) was performed in the apical four-chamber view with the sample volume placed in the mitral valve orifice at the level of the leaflet tips as imaged during mid-diastole. Mitral flow velocity measurements were made
from the cycles which exhibited the narrowest spectral dispersion and the highest peak velocity in early diastole. Evaluation of mitral annular motion using Tissue Doppler Imaging and examining the relationship of the amplitude of E/ e’ was performed per recommendation of the most recent ASE guidelines. LA volume was determined from apical 2- and 4-chamber views and indexed to BSA. Diastolic dysfunction was graded following an algorithm that combined ASE and Redfield criteria using three echocardiographic parameters: E/A ratio, E/e’ ratio and the left atrial volume index (LAVI) using the algorithm in figure 1.

Statistical Analysis

Descriptive statistics were generated overall and by 6-level parity for the analytic sample. Weighted means and standard errors were reported for continuous variables and weighted frequencies for categorical variables. Sample weights were incorporated by calibration to the 2010 census characteristics by age, sex, and Hispanic background in each study site target population. Bivariate associations between baseline characteristics and parity were assessed using survey linear regression models and chi square tests. These models adjust for sampling weights calibrated to the 2010 census.

We will use multi-level, multivariable survey logistic regression models to assess the relationship between parity and the presence of abnormal LV geometry and any grade diastolic dysfunction (grades I-III). Comparable multivariable survey linear regression models were used to assess the relationship between parity and end diastolic volume (EDV), end systolic volume (ESV), LAVI, LVM and EF. The models were adjusted for covariates as follows:

Model 1: Age

Model 2: BMI, SBP, Diabetes, anti-hypertensive medication use in addition to variable in model 1
Model 3: Smoking status, total and HDL cholesterol in addition to variables in model 2

Model 4: Education and income in addition to variables in model 3

Here we will display our preliminary results for these 4 models.

Beta estimates and standard errors are reported for linear models, as well as odds ratios and 95% confidence intervals for categorical measures. Percentage of participants with diastolic dysfunction by parity levels are represented using a bar chart. A p-value of >0.05 was considered statistically significant and all analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

Preliminary Results

Subjects

In the target population, 5.0% were nulliparous (no live births) and 10.5% were grand multiparous (≥5 live births). Baseline characteristics are detailed in table I. A larger number of births was predictive of a higher BMI, lower educational attainment, and less income. Current smoking rates varied greatly with level of parity. Women with more births had a higher SBP and greater likelihood of diabetes.

Linear Regression Models - Cardiac Volumes, LV Mass and Systolic Function

Women within all categories above 2 or more live births had significantly higher LV EDVs compared to nulliparous women with volumes 7.6 to 8.8 mL higher in these categories compared to nulliparous women in age adjusted models as summarised in table II (model 1). Interestingly, women with 2 or more live births had significantly higher volumes compared to both nulliparous categories as well as the category with 1 live birth but the EDV did not significantly increase from 2 or more live births onwards. Similarly women with all categories above 2 or more live
births had significantly higher LV ESVs compared to nulliparous women with volumes 3.3 to 4.3 mL higher in these categories compared to nulliparous women in age adjusted models as summarised in table II. LAVI was also higher with 4 or more live births compared to nulliparous women by approximately 3mL/m². All these associations remained statistically significant in fully adjusted models for age, BMI, DM or pre-diabetes, SBP, use of anti-hypertensive medications, smoking, total and HDL cholesterol as well as SES as shown in table II.

LVM was significantly higher in women with 2, 4 or ≥5 live births compared to nulliparous women, with mass as much as 27 gms higher in women with 4 live births in age adjusted models as summarised in table II. Even in fully adjusted models for age, BMI, DM or pre-diabetes, SBP, use of anti-hypertensive medications, smoking, total and HDL cholesterol as well as SES mass remained as much as 20 gms higher in women with 4 live births or more. For unclear reasons, women with 3 live births did not have significantly higher mass compared to nulliparous women. Ejection fraction was not significantly associated with parity.

**Logistic Regression Models - LV Geometry and Diastolic Dysfunction**

When LV geometry was categorized as normal vs abnormal, overall 45% of the women had abnormal LV geometry but this was not significantly associated with parity. The overall prevalence of any grade diastolic dysfunction in the target population was 65%. Among the nulliparous women, 53% had any grade diastolic dysfunction as compared to 59-66% of women with 1-4 live births and 85% of women with ≥5 live births (p=0.006). In a multivariable logistic regression model adjusted for age the odds ratio for any grade diastolic dysfunction in grand-multiparous women compared to nulliparous women was 3.9 (95% CI 1.7 – 9.3, p=0.002) as shown in figure 2. There was also a trend towards higher prevalence of diastolic dysfunction in women with 1-4 live births compared to nulliparous women though this did not reach statistical significance – odds ratio of 1.7 (95% CI 0.9 – 3.2, p=0.1). In a models adjusted for age, BMI, DM
or pre-diabetes, SBP, use of anti-hypertensive medications, smoking, total and HDL cholesterol the odds ratio for any grade diastolic dysfunction in grand-multiparous women compared to nulliparous women was still 3.1 (95% CI 1.3 – 7.2, p<0.01). This association remained essentially unchanged after further adjustment for education and income as a proxy for socio-economic status.

**Conclusions**

High parity may be associated with increased LV mass, LV and LA volumes as well as the presence of diastolic dysfunction among Hispanic/Latina women. Further studies are needed to determine the pathophysiology for the apparent deleterious consequences on the LV and its diastolic function and whether these changes translate into heart failure with preserved ejection fraction. If parity is truly a novel risk factor for HFpEF and CVD, the underlying mechanisms need to be studied to determine if there are any potential preventive strategies.
References


7. Clapp JF, 3rd, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol*. 1997;80:1469-1473


14. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: A report from the American society of
echocardiography’s guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*. 2005;18:1440-1463


Table I: Baseline Characteristics (Frequency or mean (se))

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Overall N=1172</th>
<th>0 Births N=69 (5.0%)</th>
<th>1 Birth N=154 (13.5%)</th>
<th>2 Births N=339 (32.3%)</th>
<th>3 Births N=304 (25.3%)</th>
<th>4 Births N=177 (13.4%)</th>
<th>5+ Births N=129 (10.5%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=56.1 (0.5)</td>
<td>56.1 (1.2)</td>
<td>54.0 (0.7)</td>
<td>55.4 (0.8)</td>
<td>56.2 (1.4)</td>
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<td>60.7 (1.1)</td>
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<td>BMI (kg/m2)</td>
<td>31.0 (0.3)</td>
<td>30.3 (0.9)</td>
<td>29.9 (0.5)</td>
<td>30.4 (0.4)</td>
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<td>32.1 (0.5)</td>
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<td>Less than HS</td>
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<td>23.3</td>
<td>21.9</td>
<td>20.7</td>
<td>36.5</td>
<td>54.5</td>
<td>62.3</td>
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<td>HS or equivalent</td>
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<td>30.1</td>
<td>21.4</td>
<td>20.4</td>
<td>23.0</td>
<td>16.1</td>
<td>18.1</td>
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<td>Greater than HS</td>
<td>45.3</td>
<td>46.6</td>
<td>56.7</td>
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<td>29.4</td>
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<td>&lt;$20,000</td>
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<td>49.5</td>
<td>53.5</td>
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<td>$20,000-$40,000</td>
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<td>37.5</td>
<td>17.3</td>
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<td>&gt;$40,000</td>
<td>11.2</td>
<td>18.3</td>
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<td>13.5</td>
<td>13.1</td>
<td>9.0</td>
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<td>Current Smoker</td>
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<td>17.3</td>
<td>21.2</td>
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<td>22.7</td>
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<td>SBP (mmHg)</td>
<td>134.3 (0.9)</td>
<td>130.2 (2.5)</td>
<td>130.5 (1.9)</td>
<td>132.8 (1.2)</td>
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<td>Non-diabetic</td>
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<td>38.5</td>
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<td>25.1</td>
<td>32.9</td>
<td>19.6</td>
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<td>40.0</td>
<td>51.2</td>
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<td>45.5</td>
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<tr>
<td>Diabetic</td>
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<td>16.3</td>
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<td>Anti-HTN meds</td>
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<td>Total Cholesterol (mg/dL)</td>
<td>214.2 (1.7)</td>
<td>223.0 (7.8)</td>
<td>216.3 (3.9)</td>
<td>214.0 (3.1)</td>
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<td>HDL Cholesterol (mg/dL)</td>
<td>53.5 (0.5)</td>
<td>54.7 (1.7)</td>
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<td>51.9 (1.5)</td>
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* P-value from survey linear regression models for continuous measures and chi square tests for categorical measures
Table II: Multi-level multivariable adjusted linear regression estimates examining association of parity with cardiac volumes and mass.

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<tr>
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<th>Parity</th>
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<tr>
<td></td>
<td></td>
<td>≥5 vs 0</td>
<td>4 vs 0</td>
<td>3 vs 0</td>
<td>2 vs 0</td>
<td>1 vs 0</td>
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<tr>
<td></td>
<td></td>
<td>estim</td>
<td>p-value</td>
<td>estim</td>
<td>p-value</td>
<td>estim</td>
<td>p-value</td>
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<td>EDV* (mL)</td>
<td>Model 1</td>
<td>8.83 (3.2)</td>
<td>0.01</td>
<td>8.42 (3.1)</td>
<td>0.01</td>
<td>8.45 (3.4)</td>
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<td>Model 2</td>
<td>7.00 (2.6)</td>
<td>0.01</td>
<td>6.31 (2.5)</td>
<td>0.01</td>
<td>7.17 (2.4)</td>
<td>0.00</td>
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<tr>
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<td>Model 3</td>
<td>7.11 (2.6)</td>
<td>0.01</td>
<td>6.02 (2.4)</td>
<td>0.01</td>
<td>7.34 (2.3)</td>
<td>0.00</td>
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<td></td>
<td>Model 4</td>
<td>8.27 (2.9)</td>
<td>0.00</td>
<td>6.29 (2.5)</td>
<td>0.01</td>
<td>7.28 (2.3)</td>
<td>0.00</td>
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<td>ESV* (mL)</td>
<td>Model 1</td>
<td>4.30 (1.4)</td>
<td>0.00</td>
<td>3.46 (1.2)</td>
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<td>0.02</td>
<td>2.27 (1.1)</td>
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<td>2.41 (1.0)</td>
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<td>Model 3</td>
<td>3.12 (1.3)</td>
<td>0.02</td>
<td>2.09 (1.0)</td>
<td>0.04</td>
<td>2.52 (1.0)</td>
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<td>Model 4</td>
<td>3.12 (1.4)</td>
<td>0.03</td>
<td>1.94 (1.1)</td>
<td>0.07</td>
<td>2.34 (1.0)</td>
<td>0.02</td>
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<tr>
<td>LAVI* (mL/m²)</td>
<td>Model 1</td>
<td>3.19 (1.3)</td>
<td>0.02</td>
<td>3.50 (1.3)</td>
<td>0.01</td>
<td>2.00 (1.2)</td>
<td>0.09</td>
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<tr>
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<td>2.68 (1.3)</td>
<td>0.05</td>
<td>3.26 (1.3)</td>
<td>0.01</td>
<td>1.75 (1.2)</td>
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<td>2.70 (1.3)</td>
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<td>3.21 (1.3)</td>
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<td>1.81 (1.2)</td>
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<td>2.69 (1.4)</td>
<td>0.06</td>
<td>3.10 (1.4)</td>
<td>0.03</td>
<td>1.81 (1.2)</td>
<td>0.14</td>
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<tr>
<td>LVM* (gm)</td>
<td>Model 1</td>
<td>24.85 (7.9)</td>
<td>0.00</td>
<td>26.68 (6.0)</td>
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<td>7.53 (4.8)</td>
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<tr>
<td></td>
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<td>17.04 (6.5)</td>
<td>0.01</td>
<td>19.60 (4.9)</td>
<td>0.00</td>
<td>2.63 (5.5)</td>
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<tr>
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<td>16.64 (6.6)</td>
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<td>19.38 (5.1)</td>
<td>0.00</td>
<td>2.75 (5.6)</td>
<td>0.62</td>
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<tr>
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<td>15.20 (6.7)</td>
<td>0.02</td>
<td>20.01 (5.4)</td>
<td>0.00</td>
<td>2.50 (5.5)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

* EDV: end diastolic volume; ESV: end systolic volume; LAVI: left atrial volume index; LVM: left ventricular mass
Figure 1. Grading of Diastolic Dysfunction in Echo-SOL
Figure 2. Prevalence of any-grade diastolic dysfunction by parity
Shivani R Aggarwal

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Education

• Primary Education in Oxford, UK.

• Higher secondary education from Sri Sathya Sai Higher Secondary School, Prashanthi Nilayam, India.

• Medical School: Adichunchanagiri Institute of Medical Sciences, Bellur, affiliated to Rajiv Gandhi University of Health Sciences, recognized by Medical Council of India, New Delhi and General Medical Council, London. Degree obtained Bachelor of Medicine and Bachelor of Surgery (MBBS). Attendance dates September 2000- May 2006.

• Internship: Completed PGY-1 of Categorical Residency in Internal Medicine at Creighton University, Omaha NE. Dates July 2009-June 2010.

• Residency: Completed PGY2-3 of Categorical Residency in Internal Medicine at Medical University of South Carolina, Charleston, SC. Dates July 2011-June 2013

Board certifications

• American Board of Internal Medicine: Certification date August 21st 2013.

• ECFMG: Certification date September 2008. Valid Indefinitely.
USMLE Scores:

- Step 1 (March 2008): Score 242/99
- Step 2 CS (May 2008): Passed
- Step 3 (December 2008): Score 218/92

Research Interests

- Parity and Cardiovascular Disease
- Rheumatic Heart Disease
- Non-invasive Cardiac Imaging
- Adult Congenital Cardiac Disease

Prior Research Experience

- Research Trainee, Department of Cardiac Radiology, Mayo Clinic, Rochester MN. Dates July 2010-June 2011. Mentor: Dr. Philip A. Araoz.

Current Research Projects

- Evaluation of Relationship between Parity and Cardiovascular
- Screening for Rheumatic Heart Disease in India

Publications and Presentations

Oral Presentations:


Poster Presentations:


Bibliography


Professional Memberships

- American Heart Association 2013 - present
- American College of Cardiology 2013 - present
- American College of Physicians 2009 – 2013

Honors and Awards

- 2000 All-India Gold Medal and Department of Biotechnology scholarship from the Government of India for outstanding performance in biology.
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