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ORIGINAL RESEARCH

CARDIOOBSTETRICS

Reproductive Factors Linked With Myocardial Fibrosis

MESA (Multi-Ethnic Study of Atherosclerosis)

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ABSTRACT

BACKGROUND Recent evidence has shown that reproductive factors are associated with an increased risk of heart failure with preserved ejection fraction in women. However, the pathogenic pathways underlying this relationship are unclear. Subclinical myocardial fibrosis has been found to be a common pathway in a large proportion of patients with heart failure with preserved ejection fraction.

OBJECTIVES This study examined the relationship between vital reproductive factors (parity, pregnancy, age at menopause, and use of hormone replacement therapy [HRT]) with interstitial myocardial fibrosis (IMF) and myocardial scar measured by cardiac magnetic resonance imaging (CMR) T1 mapping and late gadolinium enhancement, respectively.

METHODS There were 596 female participants (mean age 67 ± 8 years) enrolled in MESA (Multi-Ethnic Study of Atherosclerosis) who had complete parity data and underwent CMR. Parity was categorized as 0 live births, 1 to 2, 3 to 4, and ≥5 live births. Multivariable regression models were constructed to assess the associations of parity status, history of null gravidity, age at menopause and HRT with CMR obtained measures of IMF (extracellular volume [ECV], native-T1 time) and myocardial scar.

RESULTS Women with a history of nulliparity had greater ECV% ($\beta = 0.95 \pm 0.28$, $P = 0.001$) and native-T1 ms ($\beta = 10.6 \pm 4.9$, $P = 0.03$) than those who had 1 to 2 live births. These associations were independent of age, traditional cardiovascular risk factors, and interim cardiovascular events. Similar associations were found for women with a history of null gravidity compared to those with a history of pregnancy (ECV% [$\beta = 0.7 \pm 0.3$, $P = 0.02$] and native-T1 ms [$\beta = 10.6 \pm 5.2$, $P = 0.04$]). There was no association between age at menopause and HRT with markers of IMF. There were no associations between parity status, null gravidity, and age of menopause with the presence of myocardial scar; however, those who used HRT were independently associated with a lesser risk of myocardial scar (OR: 0.20; 95% CI: 0.05-0.82).

CONCLUSIONS In a multiethnic cohort, women with a history of nulliparity or null gravidity had greater IMF defined by CMR, while those who used HRT were less likely to have myocardial scar. (JACC Adv 2023;2:100703) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CVD = cardiovascular disease

ECV = extracellular volume

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HRT = hormone replacement therapy

IMF = interstitial myocardial fibrosis

LGE = late gadolinium enhancement

PMW = postmenopausal women

The prevalence of heart failure with preserved ejection fraction (HFpEF) has increased in the last decades and is higher among women than men.[1,2] Among women, recent evidence has shown an increased risk of cardiovascular disease (CVD) and heart failure (HF) among those with reproductive risk factors (premature menopause, polycystic ovary syndrome, nulliparity, multiparity, pregnancy loss, etc).[3-5] In this regard, a recent longitudinal study from the Women's Health Initiative (WHI) found a higher risk of incident HFpEF among women with a history of nulliparity, as well as among those with shorter total reproductive duration (ie, menarche to menopause).[3] Importantly, a more recent prospective study found that a history of female infertility was associated with a 27% higher risk of incident HFpEF.[4] However, other studies evaluating the relationship between parity and CVD have shown conflicting results, and this issue therefore remains controversial requiring more detailed investigation.[6,7]

On the other hand, studies on the use of hormone replacement therapy (HRT) in postmenopausal women have shown conflicting results.[8] While in a different study of postmenopausal women, WHI investigators found that HRT use did not reduce the risk of incident HF or HF hospitalization,[9] other studies have suggested otherwise.[10]

Subclinical interstitial myocardial fibrosis (IMF) is considered one of the most critical pathophysiologic mechanisms contributing to HFpEF. With advanced contrast-enhanced magnetic resonance imaging, we can measure IMF noninvasively. IMF can be assessed by CMR defined extracellular volume (ECV) fraction and native T1 measurements.[11]

To our knowledge, no clinical studies have investigated the potential link between reproductive factors with myocardial fibrosis development, an established substrate for HFpEF and end-stage HF. We used data from the MESA (Multi-Ethnic Study of Atherosclerosis) to assess the associations of parity status, history of null gravidity, age at menopause, and use of HRT with both IMF and prevalence of myocardial scar. We hypothesize that female participants who were either nulliparous, had a history of null gravidity, had an earlier age at menopause, or did not use HRT have CMR parameters that reflect a greater degree of IMF and a higher prevalence of myocardial scar.

METHODS

STUDY POPULATION. MESA aims to discover the prevalence and markers of subclinical CVD. It included 6,814 participants from multiple ethnicities/races free of clinical CVD at the baseline exam. The MESA started its recruitment in 2000, and to date, 6 follow-up visits have been completed. The recruitment process for visit 1 occurred between 2000 and 2002 in sites in the United States. Subsequently, 3,015 individuals underwent cardiac magnetic resonance imaging in visit 5 (2010-2012). The Institutional Review Boards approved the study protocol of participating institutions, and each participant signed informed consent before recruitment.[12] Demographics and clinical characteristics of participants enrolled in the MESA have been described previously.[12] T1 mapping with late gadolinium enhancement (LGE) using the modified look-locker inversion recovery sequence was performed on 1,345 participants at 5 field centers. Of these participants, 596 of the female sex who had available data on live births and answered the survey about whether they were ever pregnant were included. Participants with missing covariates and CKD were excluded. Data on participants that had a history of ever using HRT and knew their age at menopause were available in 523 and 457 women, respectively.

ASSESSMENT OF PARITY STATUS, PREGNANCY, AGE AT MENOPAUSE, USE OF HORMONE REPLACEMENT THERAPY, AND OTHER COVARIATES. Variables of interest (parity status, pregnancy, age at menopause, and use of HRT) were based on self-reported surveys collected on the initial MESA examination in 2000 to 2002. Parity status, history of pregnancy, age at menopause, and use of HRT were considered independent variables. The definition of parity included the number of total live births, while the history of gravidity was defined as "ever been pregnant." Previous studies have shown excellent validity between chart reviewing medical records and self-reported parity surveys.[13] As shown in previous studies and given that cardiovascular risk follows a J-shaped trajectory with parity status, we divided parity into 0 live births or nulliparity, 1 to 2 live births (as reference), 3 to 4 live births, and ≥5 live births.[6,14,15] Previous studies from the MESA have established a well-defined algorithm to identify participants' parity status.[6,7] Other demographics, clinical characteristics, and medication use were collected through standardized questionnaires at exam 5.

TABLE 1 Study Population Baseline Characteristics

Age, y	67 ± 8
Body mass index, kg/m^2	28 ± 6
Race/ethnicity (%)	
White	316 (53)
Black	135 (23)
Chinese	70 (12)
Hispanic	75 (12)
Null gravidity (%)	89 (15)
Number of live births (%)	
0	128 (21.5)
1-2	257 (43)
3-4	164 (27.5)
≥5	47 (8)
Age of menopause, y (available in 457 participants)	48 ± 6
Use of hormone replacement therapy (available in 523 participants)	314 (60)
Current smoking (%)	
Never	316 (53)
Former	238 (40)
Current	42 (7)
Diabetes mellitus status (%)	
None	419 (70)
Prediabetes	93 (16)
Type 2 diabetes	84 (14)
Heart rate, beats/min	65 ± 10
Systolic blood pressure, mm Hg	121 ± 20
Diastolic blood pressure, mm Hg	65 ± 9
Hypertension medication (%)	285 (48)
LDL cholesterol, mg/dL	111 ± 31
HDL cholesterol, mg/dL	60 ± 17
Any lipid-lowering medication (%)	213 (36)
eGFR ml/min/1.73 m^2	86 ± 21
LV end-systolic volume index, mL/m^2	22 ± 6
LV end-diastolic volume index, mL/m^2	62 ± 11
LV mass index, g/m^2	58 ± 9
LV ejection fraction (%)	64 ± 6
History of myocardial infarction	8 (1)
History of coronary artery disease	21 (3.5)
History of congestive heart failure	12 (2)
Extracellular volume fraction (%)	27 ± 3
Native T1 time, ms	985 ± 45
Myocardial scar (available in 523 participants)	14 (3)

Values are mean ± SD or n (%).
eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricle.

CARDIAC MAGNETIC RESONANCE IMAGING. The MESA CMR imaging details have been summarized in previous studies. All images were acquired by 1.5-T CMR machines. A cine steady-state free-precession sequence obtained 12 short-axis slices, 1 4-chamber view, and 1 2-chamber view to determine left ventricular (LV) ejection fraction, mass, and dimension indices.

Interstitial myocardial fibrosis. Assessment of diffuse IMF was determined by measuring ECV fraction (%) and native T1 (ms).[11,16] Higher ECV% and native T1 time are associated with greater diffuse IMF.[11] Measurements for T1 mapping were taken by utilizing the single breath-hold modified look-locker inversion recovery sequence in 1 midventricular short-axis section at 3 phases: precontrast and 12- and 25-minute postcontrast administration.[17] Analysis of T1 mapping was done using the QMass software. Native T1 measurements were obtained after drawing a specific area of interest within regions of the whole LV myocardium. To measure ECV, we used a synthetic ECV calculated by multiplying (1− hematocrit) with the partition coefficient (which is extrapolated by plotting 1/T1 myocardium vs 1/T1 blood at precontrast 12- and 25-minute postcontrast to get the slope of the line). There has been an excellent correlation between synthetic ECV and conventional ECV, which was shown to be associated with worse cardiovascular outcomes.[18]

Replacement myocardial fibrosis. Assessment of a region of myocardial scar or LGE was performed manually offline and quantified as a percentage of LV mass by QMass research software. The full width at half-maximum criteria of a region with increased signal intensity was defined as a myocardial scar. LGE images were taken after 15 minutes of contrast administration (0.15 mmol of intravenous gadopentetate dimeglumine). Myocardial scar was defined as hyperenhancement in either 1 short-axis and 1 long-axis image at a matching location or 2 neighboring short-axis slices.[19] We identified 14 (2.5%) participants with a myocardial scar in our sample. Ischemic myocardial scars involved the endocardium in a coronary artery distribution. Nonischemic scars mainly involved the subepicardium or midwall without having a coronary distribution. Studies that evaluated myocardial scar in MESA have been previously published.[19-21]

STATISTICAL ANALYSIS. Baseline demographics, clinical characteristics, and CMR imaging parameters were presented as mean ± SD or as median (IQR), depending on the normality of the data. In contrast, categorical variables were presented as frequencies and percentages. Multivariate linear regression was used to determine the relationship between parity status (with 1-2 live birth as reference), null gravidity, age at menopause (per 1-year increase), and use of HRT with each CMR measure of IMF (ECV% and native-T1 ms). Each parity status, history of null gravidity, age at menopause, and use of HRT were retained in all models as independent variables and the selected covariates. Regression models were analyzed as follows: model 1, an unadjusted model,

TABLE 2 Multivariable Association Between "Number of Live Births" and CMR Measures of Interstitial Myocardial Fibrosis (ECV and Native T1 Mapping)

	ECV (%)								Native T1 (ms)							
	Model 1		Model 2		Model 3		Model 4		Model 1		Model 2		Model 3		Model 4	
Number of Births	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value
0	0.97 ± 0.29	0.001	0.95 ± 0.30	0.001	0.95 ± 0.28	0.001	0.9 ± 0.3	0.002	10.1 ± 4.9	0.01	10.0 ± 4.9	0.04	10.6 ± 4.9	0.03	11 ± 5	0.03
1-2 (ref.)																
3-4	−0.03 ± 0.03	0.20	−0.08 ± 0.27	0.80	−0.09 ± 0.27	0.70	−0.1 ± 0.3	0.70	2.4 ± 4.5	0.30	1.8 ± 4.6	0.70	0.7 ± 4.6	0.90	0.4 ± 5	0.90
≥5	0.26 ± 0.42	0.20	0.30 ± 0.44	0.60	0.08 ± 0.44	0.80	0.1 ± 0.4	0.80	4.2 ± 7.2	0.20	6.1 ± 7.5	0.40	6.7 ± 7.6	0.40	3 ± 8	0.70

Model 1: Unadjusted. Model 2: Adjusted for age, race/ethnicity, waist circumference, income. Model 3: Adjusted for variables included in model 2, and lipid-lowering therapy, any hypertensive medication, ankle brachial index, diabetes status, heart rate, smoking status, estimated glomerular filtration rate, left ventricular mass index, microalbuminuria, history of coronary artery disease, and history of congestive heart failure. Model 4: Adjusted for variables included in model 3 but excluding those with interim events of myocardial infarction, congestive heart failure, and those with myocardial scar using late gadolinium enhancement.

CMR = cardiac magnetic resonance; ECV = extracellular volume.

followed by model 2, included minimal adjustment for age, race/ethnicity, waist circumference, and income, while model 3 included a fully adjusted model that had the same variables that were controlled for in model 2 as well as taking any lipid-lowering therapy, any hypertensive medication, ankle-brachial index, diabetes status, heart rate, smoking status, estimated glomerular filtration rate, microalbuminuria, LV mass index, history of coronary artery disease, and history of HF. An additional model (model 4) was constructed as a sensitivity analysis, excluding participants who had interim cardiovascular events such as myocardial infarction (MI), congestive HF, and myocardial scar. The missing data approach was complete-case analysis, which uses only participants who have all variables observed for each variable of interest since not all participants had available data on age at menopause and use of HRT. To analyze the relationship between the reproductive factors with myocardial scar, multivariate logistic regression was used, controlling for the same variables for IMF. A 2-sided $P < 0.05$ was considered statistically significant. All analyses were done using STATA-17 (StataCorp LP).

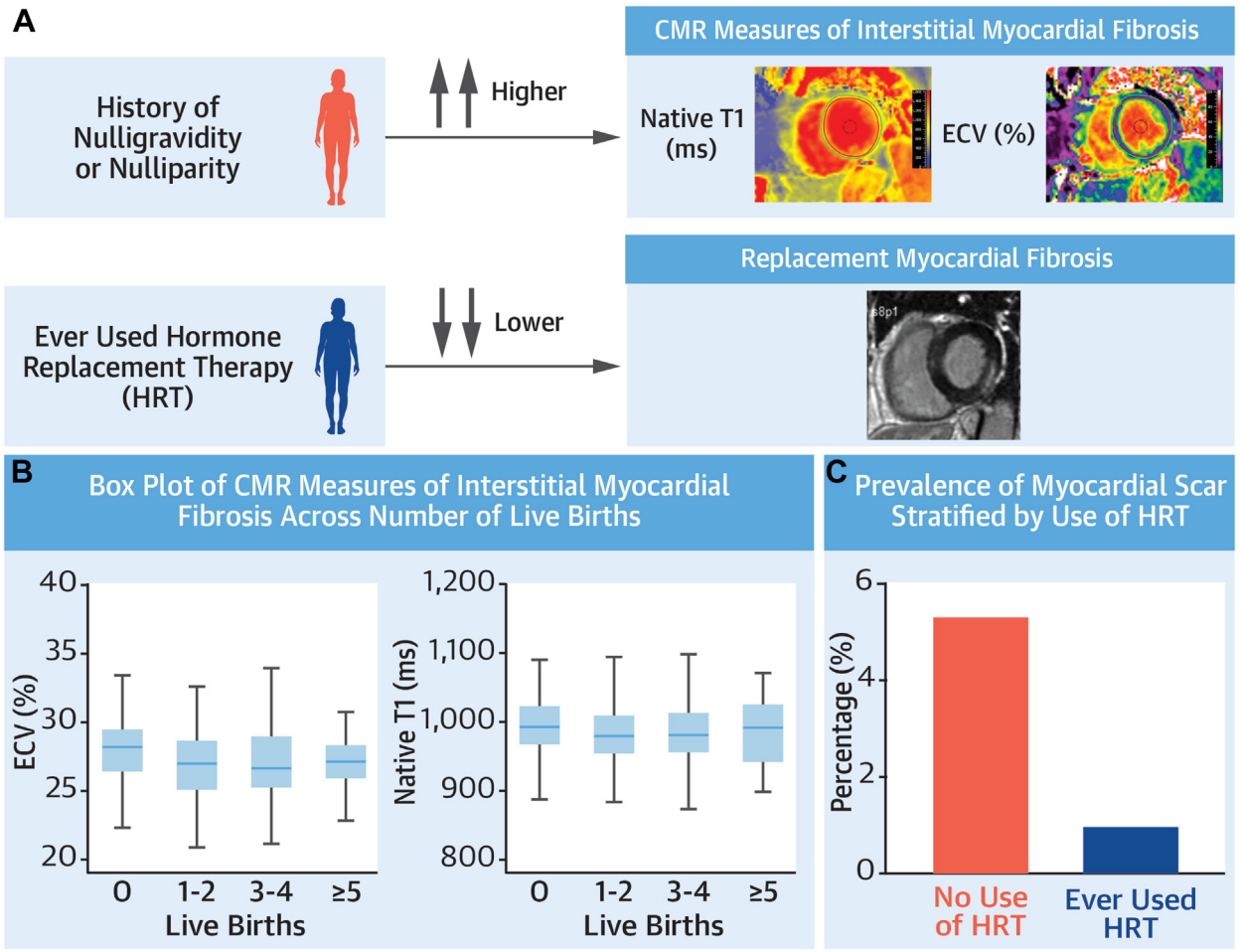
RESULTS

PARTICIPANTS CHARACTERISTICS. The characteristics of participants included in this analysis are presented in Table 1. 596 participants with completed pregnancy history also had T1 mapping and LGE assessment performed in MESA exam 5 (2010-2012). The mean age of the final sample was 67 ± 8 years, with 85% having a history of pregnancy and 21.5% having no live births. In addition, 72% reported having gone through menopause, with a mean age of 48 ± 6 years at menopause. Moreover, out of 523 participants who had available data on the use of HRT, 60% reported ever using HRT. The mean LV ejection fraction, LV end-diastolic volume index, and LV mass index were 64%, 62.2 mL/m^2, and 58 g/m^2, respectively. Mean ECV and native T1 were 27% ± 3% and 985 ± 45 ms, respectively. Other characteristics of the study cohort are shown in Table 1.

INFLUENCE OF REPRODUCTIVE FACTORS ON INTERSTITIAL MYOCARDIAL FIBROSIS. Tables 2 and 3 show ECV and native T1 according to parity status and history of ever being pregnant, respectively. Compared to participants with 1 to 2 live births, participants with 0 live births had higher ECV and native T1 in both unadjusted and fully adjusted models. Those with 0 live births had 0.95% higher ECV (adj β = 0.95; SE = 0.28; $P = 0.001$) and 10.6% higher native T1 (adj β = 10.6; SE = 4.9; $P = 0.03$). No differences were observed in ECV and native T1 between those with more than 2 live births and those with 1 to 2 live births (Table 2). Central Illustration demonstrates box plots of ECV across groups of participants classified by the number of live births, with median ECV and native T1 being highest among participants with 0 live births. The associations remained significant after excluding participants who had a history of MI, congestive HF, and myocardial scar.

Similarly, when comparing the history of pregnancy with CMR measures of IMF, individuals with null gravidity during their life course were found to have greater ECV and native T1. In the multivariable analyses, never having a history of pregnancy was an independent predictor of higher ECV (adj β = 0.7; SE = 0.3; $P = 0.02$) and greater native T1 (adj β = 10.0; SE = 5.2; $P = 0.04$) irrespective of age, ethnicity, smoking status, and antihypertensive medication, history of coronary artery disease, HF, and other clinical variables (Table 3). When evaluating age at menopause and history of ever using HRT relative to CMR measures of IMF, in all models, there were no significant associations of age at menopause or history of using HRT with ECV or native T1 (Table 3).

CENTRAL ILLUSTRATION **Association Between Nulligravidity, Nulliparity, and Hormone Replacement Therapy and Interstitial Myocardial Fibrosis and Myocardial Scar**



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Null gravidity or Nulliparity (A and B) and use of hormone replacement therapy (A to C) were associated with higher interstitial myocardial fibrosis (ECV and native T1) CMR measures and lesser risk of prevalent myocardial scar, respectively. This association was not explained by traditional cardiovascular risk factors, interim cardiovascular events, or sociodemographic factors. CMR = cardiac magnetic resonance; ECV = extracellular volume.

Similar results were obtained after excluding participants who had interim cardiovascular events (model 4).

INFLUENCE OF REPRODUCTIVE FACTORS ON REPLACEMENT MYOCARDIAL FIBROSIS. In the current sample, 14 (3%) had myocardial scars assessed by LGE. When considering the association of parity with the prevalence of replacement myocardial fibrosis or scar by LGE, there were no significant differences in the prevalence of myocardial scar according to parity status (**Table 4**). Similarly, in adjusted models, there were no associations between history of null gravidity (OR: 0.91, 95% CI: 0.13-6.50; $P = 0.90$) or age at menopause (OR: 0.94, 0.85-1.05) with replacement myocardial fibrosis (Supplemental Figure 1, **Table 5**). However, women with a history of using HRT had a lower prevalence of myocardial scar (0.95% vs 5.3%, $P = 0.003$) (Supplemental Figure 1) and reduced risk of myocardial scar in all models (**Table 5**). This finding remained significant after excluding participants who had a previous history of MI or congestive HF.

DISCUSSION

In this multiethnic community-based cohort of women free of CVD at study enrollment, we found that those with either a history of nulliparity or null

TABLE 3 Multivariable Association Between History of Never Been Pregnant, Age of Menopause, and History of Ever Using Hormone Replacement Therapy With CMR Measures of Interstitial Myocardial Fibrosis (ECV and Native T1 Mapping)

	Null Gravidity (n = 596)				Age of Menopause (n = 457)				Ever Used Hormone Replacement Therapy (n = 523)			
	ECV (%)		Native T1 (ms)		ECV (%)		Native T1 (ms)		ECV (%)		Native T1 (ms)	
Regression Models	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value
Model 1	0.6 ± 0.3	0.04	9.2 ± 5.2	0.07	−0.02 ± 0.02	0.3	0.11 ± 0.36	0.70	−0.2 ± 0.2	0.40	−4 ± 4	0.30
Model 2	0.6 ± 0.3	0.04	9.0 ± 5.2	0.09	−0.03 ± 0.02	0.1	0.05 ± 0.37	0.90	−0.3 ± 0.2	0.20	−5 ± 4	0.20
Model 3	0.7 ± 0.3	0.02	10.0 ± 5.2	0.04	−0.03 ± 0.02	0.1	0.09 ± 0.37	0.80	−0.4 ± 0.2	0.10	−6 ± 4	0.20
Model 4	0.75 ± 0.3	0.015	14 ± 5	0.01	−0.03 ± 0.02	0.2	0.2 ± 0.4	0.60	−0.3 ± 0.25	0.20	−5 ± 4	0.20

Model 1: Unadjusted. Model 2: Adjusted for age, race/ethnicity, waist circumference, income. Model 3: Adjusted for variables included in model 2, and lipid lowering therapy, any hypertensive medication, ankle brachial index, diabetes status, heart rate, smoking status, estimated glomerular fraction volume, left ventricular mass index, microalbuminuria, history of coronary artery disease, and history of congestive heart failure. Model 4: Adjusted for variables included in model 3 but excluding those with interim events of myocardial infarction, congestive heart failure, and those with myocardial scar using late gadolinium enhancement.

ECV = extracellular volume.

gravidity had greater myocardial IMF defined by CMR, including higher ECV(%) and native T1 time (ms) 10 years later. However, neither parity status nor pregnancy history was associated with the prevalence of myocardial scar, although women with a history of HRT use had a lesser risk of myocardial scar.

Emerging evidence has established cardiac sex-specific differences in pathologies between men and women. HFpEF is more prevalent among women than men. Previous work by Liu et al[22] showed that CMR parameters of IMF, postulated as a substrate for HFpEF, were greater in women but had less progression over time than in men. Similar findings were confirmed by Rosmini et al,[23] who showed higher ECV and native T1 in women than in men. Recent studies on sex-specific risk factors among women have shown that reproductive-related features might play a significant role in the pathogenesis of CVD, especially HFpEF.[3,4] A longitudinal study by Hall et al[3] from the WHI cohort that included 28,516 women found that those with a history of nulliparity had a higher incidence of HFpEF in the fully adjusted model (HR: 2.75; 95% CI: 1.16-6.52). A follow-up study from the WHI cohort found that women with a history of infertility had an increased risk of HFpEF (HR: 1.27; 95% CI: 1.09-1.48).[4] Importantly, data from the Swedish population register show a J-shaped relationship between parity and worse cardiovascular outcomes, with 0 live birth and multiple births (>2 live births) being associated with worse outcomes.[15] Our study found that nulliparity and no pregnancy history were associated with greater IMF defined by CMR T1 mapping. However, we did not find an association between increasing live births (>2) and greater IMF. These findings parallel those by Hall et al,[3] where only nulliparity was associated with HFpEF. Our results highlight the possibility that reproductive factors in women might play a vital role in the development of HFpEF. However, our study could not discern between nulliparity by choice or infertility as underlying reasons for a history of nulliparity or never being pregnant.

Several prior studies have pointed out that sex hormones might contribute to women's risk for adverse LV remodeling and HF.[24-26] A study of 2,834 postmenopausal women from the MESA by Zhao et al[26] on the role of endogenous sex hormones on the incidence of CVD found that postmenopausal women with a higher androgenic profile had an increased incidence of HF. Nevertheless, our recent study on the relationship between sex hormones and myocardial fibrosis found that endogenous sex hormones were not associated with ECV or native T1 in postmenopausal women.[27] This adds more complexity to establishing a direct relationship between reproductive factors and myocardial fibrosis; however, it is still unknown if, during pregnancy, differences in estrogen and progesterone contribute to a lower incidence of CVD. On the other hand, the link between nulliparity and null gravidity with CVD in women could be related to changes in immunity. During pregnancy, there is a reduction in natural killer cells and other inflammatory-related cells and a shift from type 1 T helper cells toward increased production of anti-inflammatory cells and regulatory T cells, and type 2 T helper cells.[28,29] Whether these changes in the immune system among those with a history of pregnancy explain the difference in the incidence of CVDs among women in the future warrants further investigations.

Several studies have found a link between earlier age of menopause and higher risk of CVD.[30] We found no significant association between age at menopause and CMR parameters of interstitial or replacement fibrosis. A pooled individual-level participant data of postmenopausal women that included 7 cohorts found that adding premature

TABLE 4 The Relationship Between Number of Live Births and the Presence of Myocardial Scar

	Myocardial Scar							
	Parity Status							
	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
0	0.86 (0.22-3.37)	0.80	0.85 (0.21-3.42)	0.80	0.67 (0.11-3.97)	0.60	0.77 (0.16-3.81)	0.70
1-2 (ref.)								
3-4	0.44 (0.09-2.15)	0.30	0.31 (0.06-1.61)	0.20	0.21 (0.02-1.64)	0.10	0.34 (0.06-2.03)	0.20
≥5	1.59 (0.3-7.89)	0.50	0.72 (0.13-4.02)	0.70	0.28 (0.03-2.58)	0.20	0.6 (0.10-4.21)	0.60

Model 1: Unadjusted. Model 2: Adjusted for age, race/ethnicity, body mass index. Model 3: Adjusted for variables included in model 2, and lipid lowering therapy, any hypertensive medication, ankle brachial index, diabetes status, heart rate, smoking status, estimated glomerular fraction volume, left ventricular mass index, microalbuminuria, history of coronary artery disease, and history of congestive heart failure. Model 4: Adjusted for variables included in model 3 but excluding those with interim events of myocardial infarction and congestive heart failure.

menopause to the "pooled cohort equations" did not improve the individual risk prediction of atherosclerotic CVD, hence highlighting that premature menopause is a marker of overall health that mediates the development of CVD through the accelerated development of cardiovascular risk factors.[31] In this regard, these findings could be related to the fact that we did not find an independent association between parity status or history of pregnancy with myocardial scar, although the prevalence of myocardial scars in the MESA cohort is significantly lower in women than in men.[19]

However, we did find that women who used HRT had a lesser risk of myocardial scar assessed 10 years later. However, studies on the use of HRT in postmenopausal women have shown conflicting results.[8] While in a different study of postmenopausal women, WHI investigators found that HRT use did not reduce the risk of incident HF or HF hospitalization,[9] other studies have suggested otherwise.[10] A longitudinal study from the UK Biobank imaging enhancement study that evaluated the use of HRT in postmenopausal women of younger age (mean age of 47 years) found that postmenopausal women that were on HRT had significantly lower LV end-diastolic volume and left maximal atrial volume.[32] A meta-analysis of 19 trials found a decrease in all-cause mortality and cardiac-related death in women that started HRT <10 years after menopause.[10] However, trials that evaluated the use of HRT among older women showed a significantly higher risk of CVD-related complications. Our findings showed a possible beneficial use of HRT in postmenopausal women. Unfortunately, data on the age at the time of HRT use were not available among all MESA participants. Studies that found protective effects of HRT were mainly seen in women who started HRT earlier after going through menopause.[33,34] In a 10-year follow-up, open-labeled, randomized controlled trial in Denmark of 1,006 women with no previous CVD (average age at inclusion and timing since menopause was 50 years and 7 months, respectively), those who were in the intervention group of HRT started early after menopause had 52% lower risk of cardiac-related mortality and admission to hospital for HF, and MI (HR: 0.48; 95% CI: 0.26-0.87; $P = 0.015$).[33] Another randomized controlled study that looked at cardioprotective effects of HRT among 643 postmenopausal women with no history of CVD, stratified by timing of menopause found a significant decrease in the progression in carotid-artery intima-media thickness among women who initiated HRT within 6 years since menopause compared to no effect among women who initiated HRT ≥10 years of menopause.[34] HRT, particularly estrogen, has been shown to exert beneficial effects on blood vessels, improving endothelial function and promoting vasodilation.[34,35] These vasoprotective effects may help maintain blood flow to the heart and reduce the risk of myocardial ischemia and subsequent myocardial scar. Secondly, estrogen has been reported to possess anti-inflammatory properties, which could contribute to a reduced risk of myocardial scar formation by mitigating inflammation and preventing the development and progression of atherosclerosis.[36] Thirdly, HRT, especially estrogen, has been found to influence lipid metabolism, leading to a more favorable lipid profile in postmenopausal women and potentially lowering the risk of atherosclerosis and myocardial scar development.[37] Lastly, HRT may influence the remodeling of the extracellular matrix, which plays a crucial role in scar formation; estrogen has been shown to modulate the expression of matrix metalloproteinases, which are involved in extracellular matrix degradation and remodeling.[36,38] It is essential to note the small number of myocardial scars in our

TABLE 5 The Relationship Between History of Pregnancy, Age at Menopause, and History of Use of Hormone Replacement Therapy With the Presence of Myocardial Scar

	Myocardial Scar					
	Null Gravidity		Age at Menopause (y)		Ever Used Hormone Replacement Therapy	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1	0.93 (0.20-4.25)	0.90	0.96 (0.88-1.04)	0.30	0.17 (0.05-0.62)	0.007
Model 2	1.06 (0.22-4.96)	0.90	0.97 (0.89-1.06)	0.50	0.19 (0.05-0.70)	0.01
Model 3	1.09 (0.15-7.77)	0.90	0.94 (0.85-1.05)	0.30	0.20 (0.05-0.82)	0.025
Model 4	0.88 (0.14-5.34)	0.90	0.97 (0.88-1.10)	0.50	0.21 (0.05-0.85)	0.03

Model 1: Unadjusted. Model 2: Adjusted for age, race/ethnicity, body mass index. Model 3: Adjusted for variables included in model 2, and lipid lowering therapy, any hypertensive medication, ankle brachial index, diabetes status, heart rate, smoking status, estimated glomerular fraction volume, left ventricular mass index, microalbuminuria, history of coronary artery disease, and history of congestive heart failure. Model 4: Adjusted for variables included in model 3 but excluding those with interim events of myocardial infarction and congestive heart failure.

study, and further research is needed to replicate these findings to fully understand the relationship between HRT and myocardial scar risk in postmenopausal women.

STRENGTHS AND LIMITATIONS

Our study has several strengths, including the ability to study the association of IMF and reproductive factors among an ethnically diverse group of women that were followed consistently for a significant period. In addition, we used techniques of high reliability, reproducibility, and safety in analyzing CMR measures of IMF.[39,40] Native T1 and ECV% are sensitive markers of IMF; however, they are not specific. Both may vary in response to other cardiac-related conditions such as myocardial hypertrophy, edema, etc.[39,40] Nevertheless, interim cardiovascular events since the baseline exam were controlled for in our regression analysis, and then an additional model was constructed as a sensitivity analysis excluding participants who had a history of MI, clinical HF, and presence of myocardial scar. Furthermore, endomyocardial biopsies, which are considered the reference standard to evaluate for myocardial fibrosis, were not performed. However, CMR has shown a significant correlation with biopsy-proven histological myocardial fibrosis.[11] Other limitations include the inability to draw causality between parity/pregnancy, use of HRT and myocardial fibrosis, given this was designed as an observational study. Also, self-report questionnaires during data collection are prone to recall bias which could have influenced our findings. Specific biases in cross-sectional studies, that is, selection and temporal biases must also be taken into consideration as women who reached 10 years of follow-up might have been systematically healthier than those who were not enrolled or lost to follow-up. Furthermore, pregnancy-related data such as: cardiovascular health during pregnancy, having undergone breastfeeding, the timing of the use of HRT, and causes of pregnancy loss were not available in the MESA. Lastly, we acknowledge that the proportion of women taking HRT (60%) in our study exceeds contemporary HRT use, and the enrollment of these patients in MESA aligns with the publication of the WHI trial.[41] As a result, our study may not accurately represent current HRT use patterns in contemporary practice. Consequently, our findings may not be directly generalizable to current HRT use patterns, given the shifts in clinical practice and patient preferences following the WHI trial. To confirm our findings, further research using other population cohorts reflecting contemporary HRT practices is necessary. An additional limitation is the small sample size, which might have accounted for wide confidence intervals for our estimations. This small sample size may limit the generalizability of our findings and could potentially lead to unstable estimations. As such, further research with a larger sample size is necessary to validate these findings.

CONCLUSIONS

In a multiethnic group of women, we found that having a history of nulliparity or no pregnancy was associated with higher CMR measures of IMF, and those who used HRT had a lesser risk of myocardial scar. These associations were independent of age, race, traditional cardiovascular risk factors, and interim cardiovascular events. Such findings add valuable information to potential mechanisms behind reproductive factors and CVD in women. Additional studies are warranted to address whether early preventive measures focused on women of reproductive age would be associated with lower interstitial and replacement fibrosis and a lower risk of cardiovascular events in the future.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This paper investigates the association between vital reproductive factors (number of live births, history of pregnancy, age at menopause, and use of hormone replacement therapy) and myocardial fibrosis (interstitial and replacement fibrosis) assessed by cardiac magnetic resonance imaging. We found that women with a history of nulliparity or null gravidity were associated with higher CMR measures of interstitial myocardial fibrosis, and those who used HRT had a lesser risk of myocardial scar. These associations were independent of age, race, traditional cardiovascular risk factors, and interim cardiovascular events. These findings support the plausible link between reproductive-related factors and subclinical markers of cardiovascular disease.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the mechanisms linking endogenous sex hormones and the effect of pregnancy and other reproductive related factors during a woman's reproductive years to heart failure risk after menopause.

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APPENDIX For supplemental figure, please see the online version of this paper.