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ORIGINAL RESEARCH ARTICLE

The effect of parity on exercise physiology in women with heart failure with preserved ejection fraction

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Abstract

Aims Women are overrepresented amongst patients with heart failure with preserved ejection fraction (HFpEF); however, the underpinning mechanism for this asymmetric distribution is unclear. Pregnancy represents a potential gender-specific risk factor for HFpEF. It leads to significant physiological adaption, and increasing parity has been associated with some cardiovascular risk. We sought to examine the relationship between prior parity with the rest and exercise haemodynamic and echocardiographic profile of women with HFpEF.

Methods and results Patients referred for assessment of exertional dyspnoea and confirmed to have a haemodynamic and clinical profile consistent with HFpEF were included. Detailed evaluation consisted of rest and exercise right heart catheterization and echocardiography. A socio-economic and obstetric history was also documented. Fifty-eight women were assessed and categorized as having either 0–2 births or ≥3 births, dividing the cohort equally. Women with ≥3 births achieved a lower symptom-limited workload than those with 0–2 births [38 (24–51) vs. 46 (31–68) W, P = 0.04]. Women with ≥3 births had a greater rise in pulmonary capillary wedge pressure indexed to workload with exercise [0.5 (0.3–0.8) vs. 0.3 (0.2–0.5) mmHg/W, P = 0.03], paralleled by a greater rise in right atrial pressure [10 (8–12) vs. 7 (3–11), P = 0.01]. Pulmonary vascular resistance was also higher in women with ≥3 births [1.9 (1.6–2.4) vs. 1.6 (1.4–1.9) mmHg/L/min rest, P = 0.046, and 1.9 (2.4–2.4) vs. 1.4 (1–1.8) mmHg/L/min exercise, P = 0.024]. Left ventricular ejection fraction was lower at rest [60 (57–61) vs. 63 (60–66), P = 0.008] and during exercise [65 (62–67) vs. 68 (66–70), P = 0.038] in women with higher parity.

Conclusions Higher parity is associated with greater impairments in multiple physiologic parameters of HFpEF severity in women, including diastolic reserve, pulmonary vascular resistance, and systolic dysfunction.

Keywords Pregnancy; Parity; Heart failure with preserved ejection fraction; Sex characteristics; Haemodynamics

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is rapidly becoming the most common form of heart failure. Whilst a key element of its diagnosis includes a left ventricular ejection fraction (LVEF) >50%, the pathophysiology is complex.[1] Key features include abnormal left ventricular diastolic performance, abnormal left atrial stiffness, and reduced systemic and pulmonary vascular compliance, although considerable phenotypic variation is recognized. Advancing age, hypertension, obesity, and diabetes are common features.[2] Notably, all large clinical trials of HFpEF have consistently demonstrated overrepresentation of women[3,4] who are conversely far less likely to develop heart failure with reduced ejection fraction.[5] To date, HFpEF clinical trials have been largely neutral; however, it is possible that specific sub-phenotypes, including female and male genders, might respond differentially to specific therapies.[6] As such, understanding the mechanism that accounts for the gender imbalance in HFpEF is potentially of major clinical and therapeutic importance.

Women face unique haemodynamic challenges with pregnancy, which can lead to adverse cardiac remodelling and

diastolic dysfunction, particularly in the context of repeated pregnancies.[7] Pregnancy is associated with alterations to the cardiovascular system that place significant load on the maternal heart,[8] in particular a significant increase in cardiac output. Accordingly, parity has been associated with increased long-term cardiovascular disease risk,[9–11] specifically coronary artery disease[12]; however, no study to date has examined the long-term haemodynamic consequences of multiparity in women with HFpEF.

On the basis of the cardiac remodelling impact of pregnancy, we hypothesized that women with higher numbers of pregnancies might be more likely to develop more advanced features of HFpEF if exposed to relevant risk factors. Accordingly, we compared the echocardiographic and invasive haemodynamic profiles of women with HFpEF according to their obstetric history.

Methods

Study population

The study cohort comprised women undergoing clinically indicated exercise right heart catheterization (RHC) to further investigate exertional dyspnoea after inconclusive non-invasive investigations for HFpEF. A cohort of men with HFpEF (n = 51) was also incorporated for a comparison of change in pulmonary capillary wedge pressure (PCWP) between genders and parity category. Patients were defined as having HFpEF if they had an LVEF ≥50% together with a resting PCWP ≥15 mmHg or an exercise PCWP ≥25 mmHg, according to established definitions.[13] Exclusion criteria were as follows: more than mild valvular stenosis or regurgitation; evidence of significant pulmonary disease on lung function testing or pulmonary imaging; chronic pulmonary emboli, hypertrophic cardiomyopathy; or previous heart transplantation.

Right heart catheterization protocol

Exercise RHC was performed using supine cycle ergometry as previously reported by us.[14] All measurements and exercise were performed in the un-fasted state together with regular medications. Natriuretic peptide levels were taken at rest immediately prior to RHC. A 7F Swan-Ganz catheter was inserted via the brachial or internal jugular vein under local anaesthesia. End-expiratory measurements were taken from the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position. Wedge position was confirmed by identification of the appropriate pressure waveform, with oximetric confirmation when required. Cardiac output was calculated using thermodilution, and the average of three measures taken for patients in sinus rhythm or five in atrial fibrillation. Measurements recorded non-invasively included heart rate, systemic blood pressure, and arterial oxygen saturation via pulse oximetry. Non-invasive and invasive measurements were taken at rest and at 3 min intervals during exercise until the patient reached their peak tolerated workload. An important feature of this approach is the application of a weight corrected workload protocol, comprising an initial workload of 0.3 W/kg, incrementing every 3 min until symptom limitation. Subjects were instructed to maintain a cycle cadence of 60 rpm during exercise.

Echocardiography

Transthoracic echocardiography was performed with the patient in the supine position, using a commercially available ultrasound machine (iE33, Phillips, Andover, MA) to obtain apical two-chamber and four-chamber views, together with transmitral flow and tissue Doppler measurements. The majority of patients had resting echocardiography performed immediately prior to RHC. Peak exercise images were obtained immediately prior to cessation of symptom-limited exercise, simultaneous with RHC measures.

Invasive haemodynamic and echocardiographic data are presented as raw values or indexed to body surface area as appropriate. In accordance with similar studies,[15] PCWP was indexed to workload. Pulmonary and systemic vascular compliance were calculated as the ratio of thermodilution-derived stroke volume to the pulmonary and systemic arterial pulse pressure, respectively.[16] Arterial elastance (Ea) was calculated as 0.9 × systemic systolic blood pressure divided by stroke volume.[17] End-systolic elastance (Ees) was estimated as 0.9 × systemic blood pressure divided by the left ventricular end-systolic volume. End-diastolic elastance (Ed) was estimated as the PCWP, used to estimate left ventricular end-diastolic pressure, divided by the left ventricular end-diastolic volume. The ratio of Ea to Ees was used to assess ventricular–vascular coupling.[18]

Obstetric history

Obstetric history was compiled using a questionnaire incorporating menarche and menopause, pregnancies and live births, breastfeeding, oral contraceptive, and hormone replacement therapy. A detailed socio-economic history was also obtained.

Ethics

This study was completed following approval of the Alfred Human Research Ethics Committee.

Table 1 Baseline demographics in women according to parity category

	0–2 births[19]	≥3 births[19]	*P*-value
Age (years)	71 (67–73)	75 (68–78)	0.065
BMI (kg/m^2)	30 (25–34)	30 (26–34)	0.68
BNP at rest (ng/L)	99 (50–170)	104 (74–129)	0.9
NT-proBNP at rest (ng/L)	230 (171–533)	672 (405–948)	0.44
NYHA class, %class III/IV	50%	61.5%	0.49
Total number of births	48	97	<0.001
Co-morbidities			
Hypertension, *n* (%)	21 (72%)	22 (79%)	0.82
Atrial arrhythmia, *n* (%)	14 (48%)	13 (45%)	1
Diabetes mellitus, *n* (%)	2 (7%)	5 (17%)	0.42
IHD, *n* (%)	4 (14%)	5 (17%)	1
COPD, *n* (%)	1 (3%)	4 (14%)	0.35
Current/ex-smoker, *n* (%)	7 (39%)	7 (30%)	0.81
Medications			
ACE-I/ARB (%)	45%	62%	0.29
Beta-blocker (%)	57%	31%	0.13
MRA (%)	22%	31%	0.7
Calcium channel blocker (%)	30%	35%	1
Loop diuretic (%)	13%	31%	0.25
Thiazide diuretic (%)	26%	23%	1
Aspirin (%)	44%	39%	0.94
Second antiplatelet (%)	9%	0%	0.42
Oral anticoagulant (%)	35%	42%	0.81
Statin (%)	52%	54%	1
Level of education			
High school	53%	55%	0.69
Tertiary	29%	35%	
Postgraduate	18%	10%	
Annual household income ($AU)			
<50 000	45%	47%	0.73
50 000–100 000	45%	42%	
>100 000	10%	11%	
Frequency of work			
Did not work	15%	35%	0.17
Part-time	81%	65%	
Full-time	4%	0%	

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

Statistical methods

Data are presented as mean ± standard deviation if normally distributed and median (interquartile range) if non-parametric. Student's *t*-test was used for comparisons of normally distributed data and Wilcoxon signed-rank test for non-parametric data. Categorical variables were compared using the chi-square test for independence. A two-tailed *P*-value <0.05 was considered statistically significant. A multivariate linear regression analysis was used to ascertain whether the effect of parity on haemodynamics was independent of age. All statistical analyses were performed using R (Version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

The study comprised 58 women with HFpEF. The median number of births was three, and the cohort was divided into those women with zero to two births and those with three or more births. Baseline characteristics of these two groups are identified in *Table 1*. There were no significant differences in co-morbidities or medications. Age and body mass index (BMI) were similar between the two groups. With regard to socio-economic status, there were no differences between parity groups in level of education, income bracket, or frequency of work during childbearing years.

Rest and exercise haemodynamics are detailed in *Table 2*. Women with ≥3 births achieved a lower symptom-limited workload than those with 0–2 births [38 (24–51) vs. 46 (31–68) W, $P = 0.04$]. Rest and exercise heart rate and blood pressure did not differ between groups. Right atrial (RA) pressure rose to a greater degree in women with ≥3 births [10 (8–12) vs. 7 (3–11), $P = 0.01$]. Similarly, PCWP indexed to workload was higher at exercise [0.9 (0.6–1.2) vs. 0.7 (0.4–1.1), $P = 0.05$] and rose to a greater degree in women with ≥3 births than those with 0–2 births [0.5 (0.3–0.8) vs. 0.3 (0.2–0.5), $P = 0.03$]. These findings are depicted in

Table 2 Invasive haemodynamics at rest and exercise according to parity category

	0–2 births[19]	≥3 births[19]	*P*-value
Peak workload (W)	46 (31–68)	38 (24–51)	0.04
Rest HR (b.p.m.)	67 ± 14	71 ± 15	0.29
Exercise HR (b.p.m.)	103 ± 24	100 ± 21	0.58
Rest SBP (mmHg)	147 ± 25	151 ± 23	0.48
Exercise SBP (mmHg)	177 ± 25	174 ± 28	0.64
Rest RAP (mmHg)	7 (5–9)	6 (4–8)	0.3
Exercise RAP (mmHg)	14 (12–17)	16 (13–21)	0.11
Rest mean PAP (mmHg)	20 (18–25)	21 (18–27)	0.65
Exercise mean PAP (mmHg)	43 (38–46)	45 (41–49)	0.14
PCWP at rest (mmHg)	13 (10–15)	13 (10–14)	0.53
Exercise PCWP indexed to workload (mmHg/W)	0.7 (0.4–1.1)	0.9 (0.6–1.2)	0.05
ΔPCWP indexed to cardiac output (mmHg/L/min)	4.6 (3.2–7.7)	6.9 (4.5–11)	0.03
Rest CI (L/min/m^2)	2.8 ± 0.6	2.7 ± 0.6	0.44
Exercise CI (L/min/m^2)	4.7 ± 1.2	4.3 ± 1.2	0.25

CI, cardiac index; HR, heart rate; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SBP, systolic blood pressure.

Figure 1, with *Figure 2* incorporating men to demonstrate the effect of sex and parity category on PCWP indexed to workload. The rise in PCWP with exercise indexed to the rise in cardiac output was also significantly higher in women with ≥3 births [6.9 (4.5–11) vs. 4.6 (3.2–7.7) mmHg/L/min, P = 0.03]. Un-indexed PCWP with exercise was not different between parity groups [30 (28–33) vs. 29 (26–33) mmHg, P = 0.53]. In multivariate linear regression analyses, parity category was a predictor of exercise and PCWP indexed to workload (P = 0.045 and 0.034, respectively), along with RA pressure (P = 0.016), independent of age. Cardiac index did not differ between the groups.

Echocardiographic data were available in 95% of patients, and 60% had simultaneous RHC together with rest and exercise echocardiography. For those without simultaneous studies, the interval between RHC and echocardiography was 82 (1–275) days. *Table 3* highlights echocardiographic variables according to parity category. Women with three or more births had a lower LVEF at both rest [60 (57–61) vs. 63 (60–66), P = 0.008] and exercise [65 (62–67) vs. 68 (66–70), P = 0.038], pictured in *Figure 3*. Parity category was a significant predictor of LVEF at rest (P = 0.017), independent of age; however, this could not be confirmed during exercise. Left ventricular, right ventricular and left atrial strain were not different between groups; however, strain measurements were only available for 24 (41%) of the cohort. All strain measurements were performed on echocardiograms simultaneous with RHC. Otherwise, there were no significant differences between groups in left ventricular wall thickness and end-systolic and end-diastolic diameter.

As shown in *Table 4*, greater parity was also associated with features of impaired pulmonary vascular function, in the absence of clear differences in systemic vascular properties. Pulmonary vascular resistance (PVR) was higher both at rest and exercise in women with three or more births [1.9 (1.6–2.4) vs. 1.6 (1.4–1.9) mmHg/L/min rest, P = 0.046, and 1.9 (2.4–2.4) vs. 1.4 (1–1.8) mmHg/L/min exercise, P = 0.024]; however, neither finding was independent of age. This was further reflected in a lower pulmonary compliance in women with three or more births, but only at rest [3.2 (2.8–3.8) vs. 4.1 (3.2–5.2) mL/mmHg, P = 0.009, and after adjusting for age, P = 0.049]. The ratio of mean pulmonary artery pressure to cardiac output at exercise, also reflecting pulmonary vascular abnormality, was higher in women with three or more births [5.9 (5.2–7.2) vs. 5.1 (4.1–6.2) mmHg/L/min, P = 0.02]. Arterial elastance rose to a greater degree, and end-systolic elastance rose to a lesser degree, with exercise in women with three or more births; however, this did not translate to significant differences in ventricular–vascular coupling (*Table 5*).

Other variables included in the obstetric history questionnaire including years between menopause and menarche,

Figure 1 Change in right atrial pressure, left, along with pulmonary capillary wedge pressure, right, with exercise according to parity category. PCWP, pulmonary capillary wedge pressure.

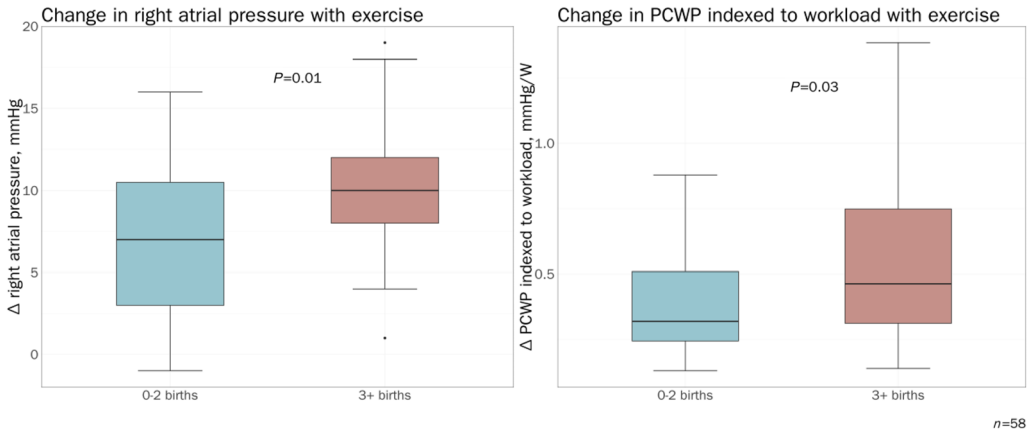

Figure 2 Change in pulmonary capillary wedge pressure with exercise indexed to workload in men and women according to parity category. PCWP, pulmonary capillary wedge pressure.

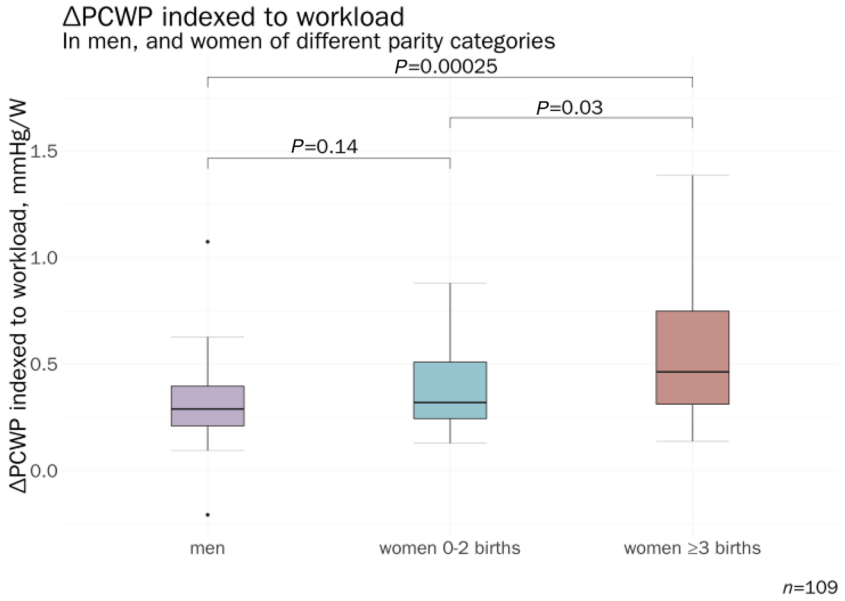

Table 3 Echocardiography at rest and exercise according to parity category

	0–2 births[20]	≥3 births[21]	*P*-value
LVEF at rest (%)	63 (60–66)	60 (57–61)	0.008
LVEF at exercise (%)[a]	68 (66–70)	65 (62–67)	0.038
LVMI (g/m^2)	84 (72–97)	79 (67–92)	0.31
End-diastolic septal wall thickness (mm)	10 (10–11)	10 (9–12)	0.8
End-diastolic posterior wall thickness (mm)	10 (9–10)	9 (9–10)	0.32
LV end-diastolic diameter	46 (43–48)	45 (43–50)	0.92
LV end-systolic diameter	29 (26–33)	31 (27–35)	0.31
LAVI	36 (30–44)	43 (32–51)	0.19
LV global strain[b]	−19 (−21 to −18)	−18 (−19 to −17)	0.2
RV global strain[b]	−19 (−24 to −19)	−19 (−21 to −15)	0.21
LA global strain[b]	24 (20–26)	22 (17–31)	0.89
RVSP at rest	28 (23–42)	34 (30–42)	0.16
TAPSE	2.3 (2.1–2.8)	2.2 (1.9–2.4)	0.36
E/e′ lateral at rest	11.6 (10–13.3)	10.3 (8.7–12.2)	0.12
E/e′ septal at rest	14.4 (12.3–17)	13.2 (11.2–19.2)	0.68
E/e′ mean at rest	12.4 (11.6–15.6)	11.3 (10.2–15.2)	0.34
E/e′ lateral at exercise[a]	12.9 (10.9–15.1)	12 (10–13.4)	0.47
E/e′ septal at exercise[a]	14.4 (12.1–15.6)	14.5 (11.9–17.2)	0.93
E/e′ mean at exercise[a]	13.7 (11.8–14.9)	13.5 (10.9–14.8)	0.68

LA, left atrial; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RV, right ventricular; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion.
[a]Exercise variables reported for 35 women with exercise echocardiography.
[b]Strain measurements were available for 24 (41%) of the cohort.

total duration of breastfeeding, weight at the time of the first pregnancy, and age at the time of first pregnancy were not independent predictors of haemodynamic variables.

Discussion

This study examined women with HFpEF with well-characterized invasive haemodynamics, echocardiography, and natriuretic peptides in the context of obstetric history. We identified several key impairments in both myocardial performance and pulmonary vascular function that related to higher parity, which could contribute to exercise intolerance in the context of a diagnosis of HFpEF. Women with an obstetric history of three or more births had a higher exercise PCWP indexed to workload along with a greater rise in PCWP indexed to workload and cardiac output with exercise, indicative of poorer diastolic reserve. This was

Figure 3 Rest and exercise left ventricular ejection fraction (LVEF) according to parity category.

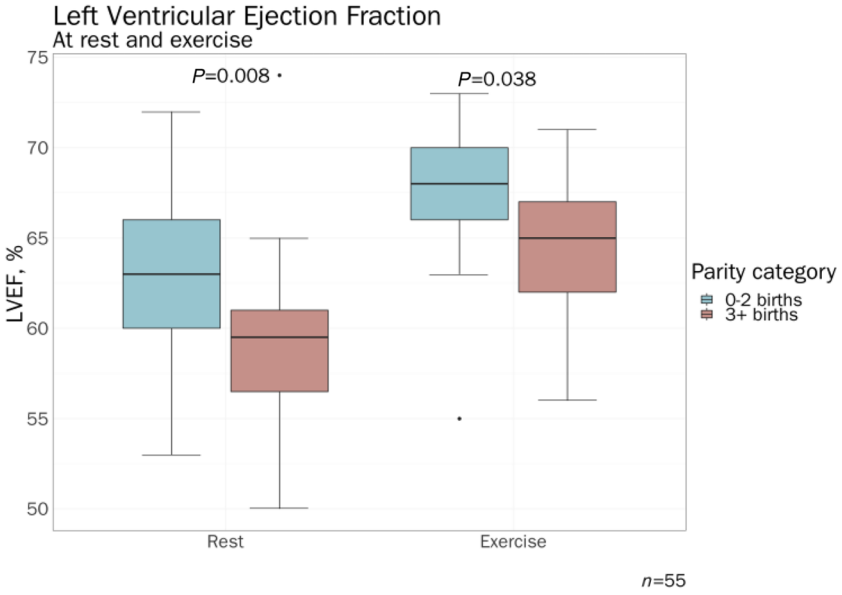

Table 4 Vascular resistance, compliance, and elastance according to parity category

	Invasively derived values		
	0–2 births[19]	≥3 births[19]	*P*-value
Rest SVR (mmHg/L/min)	18.4 ± 6.9	20.3 ± 5.4	0.24
Exercise SVR (mmHg/L/min)	11.4 (9.4–15.8)	11.5 (9.8–16.1)	0.93
Rest PVR (mmHg/L/min)	1.6 (1.4–1.9)	1.9 (1.6–2.4)	0.046
Exercise PVR (mmHg/L/min)	1.4 (1–1.8)	1.9 (2.4–2.4)	0.024
Systemic compliance at rest (mL/mmHg)	1.1 (0.9–1.3)	1 (0.8–1.2)	0.21
Systemic compliance at exercise (mL/mmHg)	1 (0.9–1.3)	1 (0.8–1.2)	0.91
Systemic compliance (mL/mmHg)	0.04 (−0.1 to 0.3)	0 (−0.2 to 0.2)	0.23
Pulmonary compliance at rest (mL/mmHg)	4.1 (3.2–5.2)	3.2 (2.8–3.8)	0.009
Pulmonary compliance at exercise (mL/mmHg)	2.5 (2.2–3.2)	2.3 (1.8–2.8)	0.15
Pulmonary compliance (mL/mmHg)	1.5 (0.8–2.1)	1.1 (0.3–1.5)	0.16
Ea at rest (mmHg/mL/m^2)	1.8 (1.4–2)	2 (1.7–2.2)	0.059
Ea at exercise (mmHg/mL/m^2)	1.8 ± 0.4	1.9 ± 0.6	0.5
Ea (mmHg/mL)	−0.09 (−0.4 to 0.09)	0.1 (−0.2 to 0.4)	0.041

Ea, arterial elastance; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Table 5 Ventricular elastance and ventricular–vascular coupling according to parity category

	0–2 births[20]	≥3 births[21]	*P*-value
Ees at rest	3.6 (2.8–4.5)	3.4 (2.7–4.2)	0.63
Ees at exercise	4.8 (4.1–7.3)	4 (3.6–5)	0.2
Ees	1.7 (1.1–2.7)	0.8 (0.4–1.3)	0.046
Ed at rest	0.1 (0.09–0.2)	0.1 (0.1–0.14)	0.63
Ed at exercise	0.3 (0.3–0.4)	0.3 (0.2–0.3)	0.63
Ed	0.2 (0.1–0.2)	0.2 (0.1–0.2)	0.89
Ea/Ees at rest	0.5 (0.4–0.6)	0.6 (0.5–0.8)	0.35
Ea/Ees at exercise	0.4 (0.3–0.4)	0.5 (0.4–0.6)	0.06
Ea/Ees	0.1 (0.09–0.19)	0.09 (0.06–0.2)	0.88

Ea, arterial elastance; Ed, end-diastolic elastance; Ees, end-systolic elastance.

accompanied by a greater rise in RA pressure with exercise and higher PVR at both rest and exercise. Women in the higher parity category also had a lower LVEF at both rest and exercise. These findings highlight a relationship between parity and greater left ventricular stiffness, pulmonary vascular and possibly right ventricular dysfunction, and impairments in systolic function (*Figure 4*).

Increased PCWP with exercise, and particularly a greater rise in PCWP with exercise, is an established feature of severity of HFpEF, which is closely linked to mortality.[15] A key component of PCWP, which reflects left ventricular end-diastolic pressure, is diastolic relaxation, impairment of which is a central feature of HFpEF.[22–24] The prominent explanation for the

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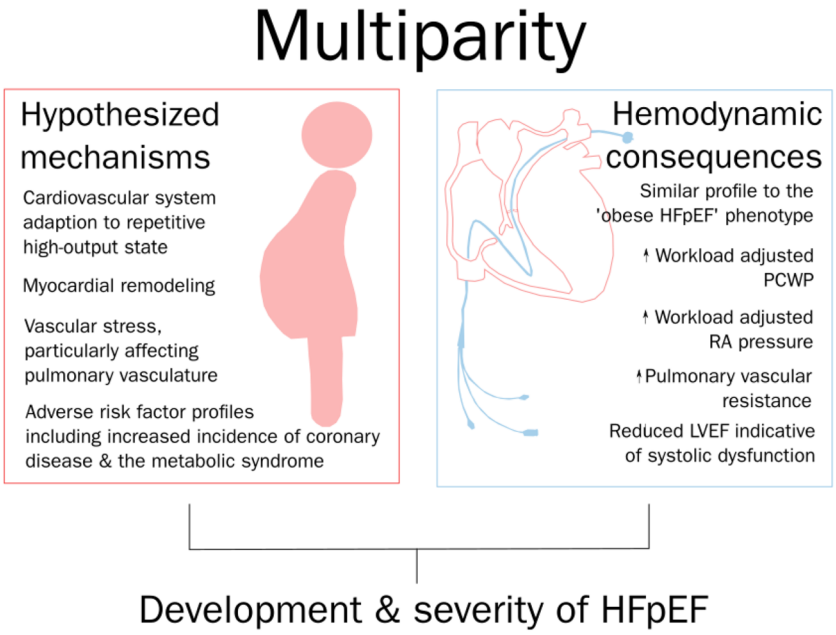
Figure 4 Proposed mechanisms behind the association between multiparity and severity of exercise limitation in heart failure with preserved ejection fraction (HFpEF). LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; RA, right atrial.



development of diastolic dysfunction in HFpEF is that co-morbidities, such as obesity, diabetes mellitus, chronic obstructive pulmonary disease, and hypertension, lead to microvascular endothelial inflammation. This, in turn, leads to both increased interstitial fibrosis and hypophosphorylation of titin, with the end result of increased ventricular stiffness.[25] It is conceivable that pregnancies could contribute to this process, with possible mechanisms including adverse lipid profiles in parous women,[9] and up-regulation of the renin–angiotensin–aldosterone system[26] and increased insulin resistance[27] in pregnancy. Furthermore, the greater risk of coronary atherosclerosis with increasing parity,[12,28] even after controlling for risk factors such as obesity and hypertension, suggests that pregnancy may have direct and lasting effects on the vasculature. This is relevant to ventricular stiffening given the role of coronary artery disease, and particularly coronary microvascular disease,[29] in the development of HFpEF.

The PCWP is determined by a composite of diastolic relaxation, compliance, and extrinsic forces.[13] Thus in conjunction with myocardial stiffness and remodelling, the PCWP also incorporates pulmonary capillary and vascular remodelling,[21] left atrial structure and function,[20] and factors external to the left ventricle including right heart–left heart interaction and pericardial restraint.[19] Similar invasive haemodynamic studies have noted a rise in RA pressure in concert with the rise in PCWP,[13,30] consistent with our findings of a greater rise in PCWP and RA pressure in women with higher parity. This supports the contribution of external factors to PCWP with exercise. Recent work has highlighted a particular 'obese' phenotype of HFpEF where those with a BMI ≥35 kg/m^2 had greater circulating volume, more concentric left ventricular remodelling, greater right ventricular dilatation and dysfunction, and increased epicardial fat thickness and greater total epicardial heart volume.[31] There were no differences between parity groups in BMI, and there is no clear mechanism for increased epicardial fat volume as a result of a higher number of births in the absence of differences in BMI; however, the haemodynamic changes and increased blood volume with repeated pregnancies could lead to similar right and left ventricular remodelling as the morbidly obese. Thus, right ventricular dysfunction and ventricular interdependence could be a key contributor to our finding of increased workload indexed PCWP in women with higher parity number.

Other haemodynamic findings in our study may lend support to a contribution of right ventricular dysfunction to exercise limitation in women with ≥3 births. Women with greater parity had higher PVR at both rest and exercise than those with zero to two births. Pulmonary compliance was lower in women with higher parity at rest and trended lower at exercise, although this was not statistically significant. Pulmonary hypertension is associated with poor prognosis in HFpEF and generally reflects duration and severity of HFpEF.[32,33] This is particularly true when the post-capillary pulmonary hypertension is combined with pre-capillary changes.[34] Women with ≥3 births had a number of haemodynamic characteristics similar to HFpEF patients with combined pre-capillary and post-capillary pulmonary hypertension, including increased PVR and a greater rise in RA pressure with exercise.[34] This could

reflect the degree of remodelling and higher exercise PCWP in women with higher parity or may suggest that repeated pregnancy could directly affect the pulmonary circulation. Changes to the pulmonary vasculature contribute to right ventricular dysfunction, and although there were no significant differences in tricuspid annular plane systolic excursion and right ventricular strain in our analysis, the trend was for poorer right ventricular function in women with ≥3 births. Right ventricular dysfunction affects substantial proportion of patients with HFpEF and is associated with poorer outcomes.[35]

Ventriculo-arterial mismatch especially due to exercise has also been suggested to contribute to the abnormal increase in PCWP in HFpEF.[36] Interestingly in this study, measures of afterload and coupling did not differ between the groups. This may suggest that the observed changes in ventricular diastolic properties were likely of a primary cause. In the current study, we did not demonstrate a difference in indirect, non-invasive measures of diastolic function, specifically E/e′. We and others have shown this measure to correlate relatively poorly with invasive haemodynamic measures.[14] Subtle systolic dysfunction has also been proposed to be present in some HFpEF patients.[37] The increment in Ees was diminished in women with higher parity, possibly suggesting that a degree of relative systolic dysfunction was present.

Taken together, women with ≥3 births have a greater rise in PCWP with exercise, which could reflect a combination of greater ventricular stiffness, pulmonary vascular remodelling, and subtle reductions in left ventricular systolic function. This array of haemodynamic changes impacts exercise tolerance, as demonstrated by achievement of a lower workload in women with ≥3 births in our study. Whilst one study has investigated the relationship between parity and HFpEF,[38] reporting an association with nulliparity and incident HFpEF, it compared only nulliparous women with those who had at least one pregnancy. Given that there is typically a J-shaped relationship between parity and cardiovascular diseases, with women who have had one to two children having the lowest risk,[12] this likely reflected increased cardiovascular risk in women with infertility, such as polycystic ovarian syndrome.[39] A relationship between parity and impaired diastolic function has been previously established,[7,40] and the haemodynamic derangements in this study expand on these findings to highlight a greater degree of exercise limitation in women with HFpEF who have higher parity.

A key strength of this study is the extent of the haemodynamic and echocardiographic characterization, at both rest and exercise. This enabled a thorough assessment of the effect of parity on multiple components of exercise physiology. Furthermore, patients were diagnosed with HFpEF according to gold-standard invasive haemodynamic criteria, with no uncertainty as to their diagnosis. Questionnaires included questions on education, work, and finances, which allowed us to ensure that associations were not due to differences in comorbidities and socio-economic status. Limitations of this study include the size of the cohort, given that the majority of recruitment was performed retrospectively, and a number of women could not be contacted. Simultaneous exercise echocardiography and strain parameters were not available in some patients due to sonographer availability and patient body habitus causing difficult imaging on the cardiac catheterization table.

Clinical implications

The present study has several potential implications. Firstly, obtaining an obstetric history may provide added insights into the understanding of factors that may have contributed to HFpEF. Although the average number of pregnancies is currently 1.7,[41] the average age and presence of comorbidities during pregnancy are rising.[42–44] If as our data suggest, the effects of pregnancy can have longer lasting effects on the heart, then it may be appropriate for at-risk patients (e.g. hypertensive, obese, and diabetic) to have closer long-term cardiovascular follow-up both during and after pregnancy. Finally, there may be a role for intensified screening for multiparous women at the time of delivery, along with cardioprotective therapy such as structured cardiac exercise programmes to prevent long-term deterioration.

Conclusion

In this invasive haemodynamic analysis of women with HFpEF, having three or more births was associated with features of more advanced HFpEF. These included greater limitation in exercise tolerance, driven by impairments in diastolic reserve, PVR, and systolic dysfunction. This is suggestive of a role of repeated pregnancies in the development and severity of HFpEF, identifying multiparous women as targets for preventative and early therapeutic measures, and may help to explain the overrepresentation of women in the HFpEF population.

Conflict of interest

None declared.

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