News in January 2024

1. Sex Differences in Clinical Outcomes Associated With Quantitative Flow Ratio–Guided PCI

BACKGROUND

FAVOR III China (Comparison of Quantitative Flow Ratio Guided and Angiography Guided PercutaneousIntervention in Patients with Coronary Artery Disease) reported improved clinical outcomes in quantitativeflow ratio (QFR) relative to angiography-guided percutaneous coronary intervention (PCI), but the clinical impact of QFR-guided PCI according to sex remains unknown.

OBJECTIVES

The authors sought to compare sex differences in the 2-year clinical benefits of a QFR-guided PCI strategy and to evaluate the differences in outcomes between men and women undergoing contemporary PCI.

METHODS

This study involved a prespecified subgroup analysis of the FAVOR III China trial, in which women and men were randomized to a QFR-guided strategy or a standard angiography-guided strategy. Sex differences in clinical benefit of the QFR guidance were analyzed for major adverse cardiac events (MACE), a composite of all-cause death, myocardial infarction, or ischemia-driven revascularization within 2 years.

RESULTS

A total of 1,126 women and 2,699 men were eligible and the occurrence of 2-year MACE was similar between women and men (10.3% vs 10.5%;P¼0.96). Compared with an angiography-guided strategy, a QFR-guided strategy resulted in a 7.9% and 9.7% reduction in PCI rates in men and women, respectively. A QFR-guided strategy resulted in similar relative risk reductions for 2-year MACE in women (8.0% vs 12.7%; HR: 0.62; 95% CI: 0.42-0.90) and men (8.7%vs 12.4%; HR 0.69; 95% CI: 0.54-0.87) (P-interaction¼0.61).

Furthermore, QFR values were not significantly different between men and women with various angiographic stenosis categories.

CONCLUSIONS

A QFR-guided PCI strategy resulted in improved MACE in both men and women at 2 years comparedwith an angiography-guided PCI strategy. The FAVOR III China Study [FAVOR III China]; (NCT03656848)

2. Female Patients With PCI Benefit From Abbreviated DAPT

TOPLINE:

Female patients at high bleeding risk (HBR) who undergo a stent implantation and receive abbreviated dual antiplatelet therapy (DAPT) don't have a higher risk for bleeding or ischemic events than male patients, despite more high-risk characteristics at baseline, results of a new study suggested.

METHODOLOGY:

- The study was a subgroup analysis of the 4579 patients enrolled in the multicenter open-label Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated vs Standard DAPT Regimen (MASTER DAPT) trial; 69.3% were male with a mean age of 76 years.
- Patients randomized to abbreviated treatment discontinued DAPT (aspirin and a platelet ADP P2Y12 receptor inhibitor) at 1 month and continued on single antiplatelet therapy (SAPT) for ≥ 6 months, except those receiving oral anticoagulation (OAC) therapy; those randomized to standard treatment continued DAPT for ≥ 2 months (except those receiving OAC) and then continued to receive SAPT for 11 months.
- Outcomes included net adverse clinical events (NACEs), a composite of death due to any cause, myocardial infarction (MI), stroke, or major bleeding; major adverse cardiac or cerebral events (MACCEs), the

composite of death due to any cause, MI, or stroke; and major or clinically relevant nonmajor bleeding (MCB), a composite of Bleeding Academic Research Consortium type 2, 3, or 5. Researchers assessed outcomes separately for male and female patients.

TAKEAWAY:

- Women were older; had higher prevalence of arterial hypertension, chronic kidney disease, and hematological or coagulation disorders; and were more likely treated with corticosteroids or nonsteroidal anti-inflammatory drugs than men.
- At 12 months, NACEs (unadjusted hazard ratio [HR], 1.02; 95% CI, 0.82-1.28; P = .83), MACCEs (unadjusted HR, 0.96; 95% CI, 0.75-1.25; P = .78), and MCB (unadjusted HR, 0.98; 95% CI, 0.78-1.23; P = .86) did not differ significantly between men and women.
- After multivariable adjustment for baseline confounders, risk for NACEs, MACCEs, and MCB remained similar between the sexes.
- There was no evidence of heterogeneity for NACEs and MCB across sexes, while abbreviated DAPT was associated with a nominal 1% increase in MACCE rates in men and more than 2% decrease in MACCE rates in women, although this should be interpreted with caution, said the authors.

IN PRACTICE:

"Our findings suggest for the first time that abbreviated DAPT should be considered for women with HBR in particular because they derive not only bleeding benefit, similarly to men, but also no discernible incremental ischemic risk compared with standard DAPT," the authors wrote.

3. Maternal and Pregnancy Outcomes Following Heart Transplantation in the US

BACKGROUND

Improved survival following heart transplantation (HT) has led to more recipients contemplating pregnancy, but data on outcomes are limited.

OBJECTIVES

The authors used a national data set to investigate and describe outcomes of pregnancies and deliveries in the United States in HT recipients.

METHODS

Diagnosis and procedure codes from the 2010-2020 Nationwide Readmissions Database identified delivery hospitalizations, history of HT, comorbid conditions, and outcomes. The authors compared rates of severe maternal morbidity (SMM), nontransfusion SMM, cardiovascular SMM (cSMM), and preterm birth from delivery hospitalization between HT recipients and no-HT recipients. The authors evaluated readmission to 330 days postpartum. Logistic and proportional hazard regressions were performed, adjusting for age, socioeconomic and facility characteristics, and clinical comorbidities.

RESULTS

Among 19,399,521 deliveries, 105 were HT recipients. Compared with no-HT, HT recipients were at higher risk for all SMM (24.8% vs 1.7%), nontransfusion SMM (20.8% vs 0.7%), cSMM (7.3% vs 0.12%), and preterm birth (43.3% vs 8.2%), all $P < 0.001$. In adjusted analyses, HT recipients had 16-fold greater odds of SMM, 28-fold greater odds of nontransfusion SMM, 38-fold greater odds of cSMM, and 7-fold greater odds of preterm birth. HT recipients had higher morbidity rates during delivery hospitalization and higher readmission rates within 1 year following delivery (26.9% vs 3.8%; adjusted HR: 6.03 [95% CI: 3.73-9.75]).

CONCLUSIONS

Delivery with history of HT is associated with significantly increased rates of SMM, preterm birth, and hospital readmission. These results provide data regarding pregnancy outcomes for use when counseling patients with HT history who are considering pregnancy or who are pregnant.

4. Impact of CAD in Women With Newly Diagnosed HFrEF

BACKGROUND

The representation of women in heart failure studies has been inadequate, resulting in a knowledge gap regarding the prognostic impact of coronary artery disease (CAD) on all-cause mortality in women with newly diagnosed heart failure and reduced ejection fraction (HFrEF).

OBJECTIVES

This study aims to assess the prognostic impact of CAD in women with HFrEF.

METHODS

Using the Western Denmark Heart Registry, the authors identified 891 women and 2,403 men referred for first-time coronary angiography because of HFrEF. The authors stratified for presence of CAD, estimated 10-year all-cause mortality, and calculated crude and adjusted HRs (aHRs) with 95% CIs.

RESULTS

The 10-year mortality was 60% in women with CAD and 27% in women without CAD; for men, the corresponding numbers were 54% and 36%. When adjusted for comorbidities, women without CAD had a lower relative 10-year mortality than men without CAD (aHR: 0.73; 95% CI: 0.58-0.91), whereas women with CAD had similar relative mortality as men with CAD (aHR: 1.00; 95% CI: 0.81-1.24) ($P_{interaction}$ = 0.037). Assessed by the number of coronary vessels with significant stenosis, CAD extent was associated with mortality for both women (P < 0.01) and men (P < 0.01). However, compared to those without CAD, the aHR was higher for women with any degree of CAD (aHR ranging from 1.61 [95% CI: 1.09-2.38] for diffuse CAD to 2.01 [95% CI: 1.19-

3.40] for 3-vessel disease) than for men with 3-vessel disease (aHR: 1.51; 95% CI: 1.19-1.91).

CONCLUSIONS

In patients with newly diagnosed HFrEF, the presence and extent of CAD has significantly greater prognostic impact among women than among men.

5. Uncovering Sex Differences in Type 2 Myocardial Infarction: Is Coronary Anatomy Enough?

Introduction

Type 2 myocardial infarction (MI) is a clinical syndrome characterized by myocardial injury that occurs in the setting of an imbalance in myocardial blood supply and demand, in the absence of plaque disruption or atherothrombosis. Since the universal definition of MI first introduced subtypes in 2007, it has become apparent that type 2 MI is underappreciated, more common than type 1 MI, and associated with substantial morbidity and mortality.[1,2] When compared to individuals with type 1 MI, those with type 2 MI tend to be older, are more likely to be female, and have a higher prevalence of cardiovascular comorbidities, such as heart failure and atrial fibrillation.[2] Yet unlike type 1 MI, for which pathophysiology is known and effective treatments are available, coronary mechanisms of type 2 MI have not been systematically elucidated. In a prior study of coronary computed tomography angiography (CCTA) in patients with type 2 MI vs type 1 MI, those with type 2 MI had smaller total, noncalcified, and low-attenuation plaque burdens than those with type 1 MI.[3] However, among patients with type 2 MI, sex-specific differences in clinical presentation and mechanism of MI have not been defined. Unfortunately, due to the deficiencies in our understanding of the pathogenesis of type 2 MI, few targeted therapies have been tested. Instead, supportive care addressing the provoking conditions of type 2 MI and management of traditional cardiovascular risk factors have remained the mainstay of treatment for type 2 MI.

In this issue of JACC: Advances, Lin et al[4] report a post-hoc analysis of sex differences in DEFINE TYPE 2 MI, a single-center prospective study of coronary anatomy among 25 males and 25 females with adjudicated type 2 MI.[5] All participants underwent CCTA during the index hospitalization for MI. Female participants with type 2 MI enrolled in the current study were significantly older than the corresponding males. Peak troponin levels were modest in both sexes (median hs-cTnT of 61 in females and 109 in males), and most participants had electrocardiogram changes or regional wall motion abnormalities by echocardiography, with or without symptoms, to fulfill the Universal Definition of MI criteria. Provoking conditions were heterogenous, and in this small cohort, cases of hypoxemic respiratory failure were numerically higher among males, while tachyarrhythmias, hypertensive urgency, and bleeding occurred in greater numbers among females. At the time of presentation, electrocardiographic ST-segment depressions were more often observed in females, while T-wave inversions were more common in males. Despite this, CCTA revealed no differences in coronary artery calcium scores by sex, and in both males and females with type 2 MI, nonobstructive coronary atherosclerosis was widely prevalent. No differences in calcified and noncalcified plaque volumes were observed in males and females. Women had lower levels of low-attenuation plaque volume, although the clinical relevance of this finding is uncertain. Perhaps most importantly, CCTA-defined obstructive coronary artery disease (CAD), defined by diameter stenosis, or hemodynamically significant lesions, assessed by FFR_{CT} ≥0.80, were identified in only a quarter of males and females with type 2 MI, with no differences by sex.

The authors should be commended for conducting a prospective imaging study of males and females with type 2 MI. Although few sex-specific differences were identified, the findings provide incremental insights to our understanding of the clinical characteristics of type 2 MI. Surprisingly, obstructive coronary artery disease was present in less than one- third of cases in both males and females, raising substantial questions as to the mechanism of ischemic imbalances in patients in the cohort who did not have

obstructive or functionally significant CAD. Unfortunately, coronary spasm testing was not performed, and spasm is well recognized as a mechanism for MI with nonobstructive coronary arteries.[6] Disorders of the microcirculation, comprised of arterioles and capillaries that cannot be visualized by CCTA, might also provoke or exacerbate imbalances in supply and demand during hemodynamic perturbations and cause type 2 MI. Without assessments for coronary spasm and microvascular dysfunction, mechanisms of type 2 MI cannot be adequately explained by plaque burden in many cases. There are other more minor limitations; coronary calcium was prevalent in this cohort, and calcium may impact the accuracy of coronary diameter assessments by CCTA and CT_{FFR}. Notably, the sample size was small and may have conferred insufficient statistical power to identify clinically meaningful sex differences in patient characteristics. Furthermore, the study enrolled a heterogenous cohort with multiple provoking causes of type 2 MI that were not matched by sex, potentially confounding sex-specific comparisons. Finally, a handful of patients with heart failure, in which the diagnosis of type MI can be challenging to adjudicate given the overlap of signs and symptoms of ischemia and volume overload, were included in the cohort.

Ultimately, this small single-center study highlights that remarkably few patients with type 2 MI have obstructive CAD, and this proportion did not differ by sex. Sex differences in plaque characteristics were modest and of uncertain clinical significance. Additional efforts are needed to understand mechanisms of type 2 MI and sex differences relevant to diagnosis and management. Larger studies incorporating coronary functional assessments in addition to coronary anatomy may be required to understand the pathophysiology of this complex and challenging MI subtype.

6. Sex Differences in Coronary Artery Disease Characteristics Among Patients With Type 2 Myocardial Infarction

Background

Type 2 myocardial infarction (MI) results from coronary supply and demand imbalance and has a poor prognosis. It is crucial to identify potential sex-based differences in the prevalence and nature of coronary artery disease (CAD) within this population.

Objectives

The purpose of this study was to evaluate sex-based disease differences in type 2 MI among patients evaluated with coronary computed tomography angiography and fractional flow reserve.

Methods

In a single-center, prospective study, patients with strictly adjudicated type 2 MI underwent coronary computed tomography angiography with fractional flow reserve.

Results

Among 50 study participants enrolled, 50% were women. A similar mix of MI precipitants was present in both sexes. ST-segment depression was more common in women (64% vs 32%), while men were more likely to have T wave inversion (68% vs 36%). Women and men had comparable coronary artery calcium scores (median: 152 [Q1, Q3: 45, 762] vs 234 [Q1, Q3: 56, 422]). Prevalence of any CAD (84% vs 100%), obstructive CAD (24% vs 28%), and hemodynamically significant focal stenosis (20% vs 32%) were similar between sexes. Total plaque volume was similar between sexes, but women had significantly lower levels of low-attenuation plaque (median: 3 [Q1, Q3: 1, 7] vs 9 [Q1, Q3: 3, 14]).

Conclusions

Among patients with type 2 MI, prevalence of any CAD and obstructive CAD did not differ according to sex. Total plaque volume was similar between sexes, but women had a lower volume of low-attenuation plaque (DEFINing the PrEvalence and Characteristics of Coronary Artery Disease Among Patients With TYPE 2 Myocardial Infarction Using CT-FFR [DEFINE TYPE2MI]; **NCT04864119**)

7. Maternal T1D, Overweight/Obesity Linked to Heart Defects in Offspring

Maternal type 1 diabetes and overweight and obesity are associated with an increased risk for congenital heart defects (CHDs) among offspring, according to a study published online Jan. 5 in JAMA Network Open.

Riitta Turunen, M.D., Ph.D., from Helsinki University Hospital and the University of Helsinki, and colleagues conducted a nationwide population-based register study in a birth cohort from Finland comprising all children born between 2006 and 2016 (620,751 individuals) and their mothers to examine the association of maternal diabetes and overweight or obesity with CHDs.

Overall, 1.7 percent of the children had an isolated CHD. The researchers found that compared with no maternal diabetes, maternal type 1 diabetes was associated with increased odds of having a child with any CHD (odds ratio, 3.77) and six of nine CHD subtypes (odds ratio range, 3.28 for other septal defects to 7.39 for transposition of greater arteries). Compared with normal maternal body mass index, maternal overweight was associated with left ventricular outflow tract obstruction and ventricular septal defects (odds ratios, 1.28 and 0.92, respectively), while obesity was associated with complex defects and right outflow tract obstruction (odds ratios, 2.70 and 1.31, respectively).

"Primary prevention of maternal overweight and obesity and careful treatment of pregestational diabetes may hold the opportunity to reduce the burden of disease," the authors write.

8. Sex-Specific Outcomes of Mitral Repair for Degenerative MR

Study Questions:

Does sex influence long-term mortality following mitral valve repair (MVr) for degenerative mitral regurgitation (MR) based on preoperative left ventricular (LV) systolic dimensions and ejection fraction (EF)?

Methods:

In a large single-center, retrospective, cohort study, consecutive patients who underwent isolated MVr for degenerative MR between 1994 and 2016 were screened. Echocardiographic parameters were obtained from the most recent study performed prior to surgery. Adjusted hazard ratios for the primary outcome measure of all-cause mortality were compared according to baseline LV end-systolic diameter (LVESD), LVESD indexed to body surface area (LVESDi), and LVEF for men and for women.

Results:

Among 4,589 patients, 1,825 (40%) were women and 2,764 (60%) were men. After a median follow-up of 7.4 years (interquartile range [IQR], 4.1-11.3) for women and 7.2 years (IQR, 3.9-11.1) for men, 344 (7.5%) patients died. Women and men had similar preoperative LVEF (59% vs. 59%, $p = 0.167$) and LVESD (3.3 cm vs. 3.4 cm, $p = 0.124$); however, women were more likely than men to have New York Heart Association (NYHA) class III-IV symptoms (37.6% vs. 23.2%, $p < 0.001$) and women had a larger LVESDi compared to men (1.9 cm/m^2 vs. 1.7 cm/m^2, $p < 0.001$). After adjusting for age, LVEF, NYHA class, year of surgery, and history of atrial fibrillation, diabetes mellitus, hypertension, and myocardial infarction, the all-cause mortality risk for women increased from the baseline hazard at an LVESD of 3.6 cm, whereas an inflection point for increased risk with LVESD was not evident for men.

The risk of mortality for women increased at LVESDi 1.8 cm/m^2 compared to 2.1 cm/m^2 in men. Women and men had a similar mortality risk inflection point of LVEF 58%; however, mortality was higher among women as LVEF decreased.

Conclusions:

After MVr for degenerative MR, women have a higher risk of all-cause mortality at lower LVESD, LVESDi, and higher LVEF. The authors conclude that these results support consideration of sex-specific thresholds for LVESDi in surgical decision making for patients with severe MR.

Perspective:

Chamber size (including chamber size indexed to body surface area) is smaller and LVEF is higher in women compared to men, and cardiac remodeling is different in women and in men. However, current guidelines for intervention for severe MR use thresholds for LV size and systolic function (LVESV ≥40 mm, LVEF <60%) that are not sex specific; and women are less likely than men to meet class I surgical thresholds. This single-center, retrospective, cohort study found that the LVESDi threshold associated with increased mortality hazard after MVr is lower in women compared to men, and the mortality risk associated with decreasing LVEF is higher in women compared to men. As the authors suggest, these data support re-examination of guideline thresholds for intervention for degenerative MR with the potential implementation of sex-specific thresholds for LV size and systolic function.

9. Gender Differences in the Cardiology Fellowship Interview Experience

Cardiology is known for its male predominance and challenging work-life balance. Survey data have indicated that female cardiologists are less likely to have children, more likely to be single, and require childcare help than males.[1] In order to mitigate gender disparities within residency and fellowship interviews, the National Resident Match Program code of conduct strongly discourages questions targeted toward individual characteristics and instead

advises focusing on personal interests and program compatibility.[2] In this study, we sought to examine the impact of gender on the interview experience among cardiology fellows across the United States.

We conducted a cross-sectional 13-question survey of cardiology fellows in 2022. The survey was created using Google Forms, and the link was sent to cardiology fellowship program coordinators and subsequently forwarded to all interviewees to be completed anonymously. Two reminder email letters were sent until the closure of the survey. The questions included demographic characteristics and social questions that might be asked during the interview process. Pearson chi-square tests were used to analyze the differences between responses provided by males and females.

Five hundred surveys were emailed, and 77 responses were received. Fifty-two males (67.5%) and 25 females (32.4%) completed the survey. Baseline demographics were similar between males and females; majority of the participants were between 30 and 45 years of age (86% vs 68%), native English speakers (69% vs 72%), American medical school graduates (65% vs 72%), and from university programs (46% vs 48%). Majority of the male and female participants were of Caucasian (36% vs 44%) and Asian (32% vs 36%) descent. We found that females were more frequently asked about their relationship status, plans for childbearing, and partner support during the fellowship with a statistically significant P value (**Figure 1**).

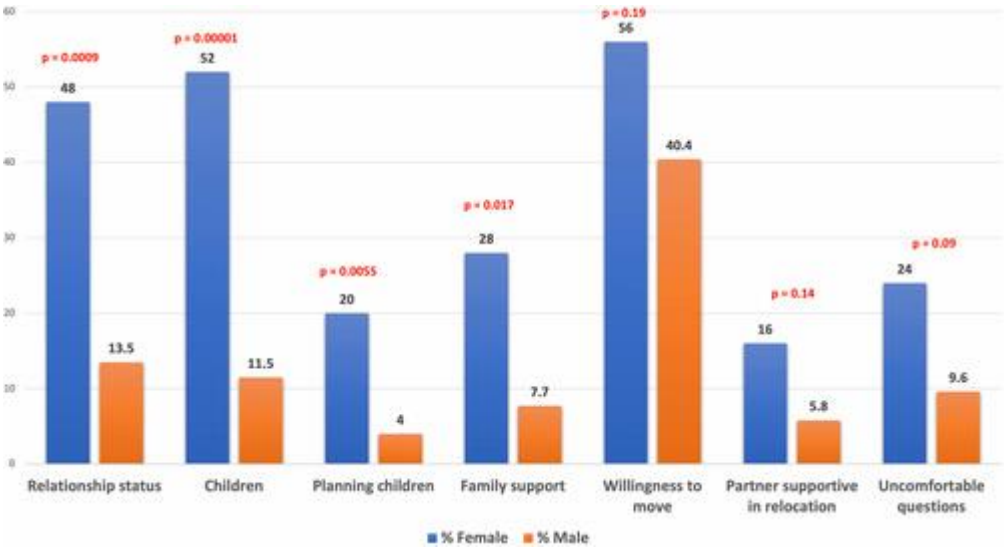

Figure 1

Graphical Representation of Survey Responses Between Males and Females

The presence of personalized family-oriented questions among both males and females signals the importance of work-life balance on the overall well-being of the candidate. Work-life balance has been conceptualized as having multiple domains including time management, fulfillment, and stress relief.[3] Directed questioning along those domains may provide better insight into a candidate's ability to navigate work-life balance. In addition, this also prompts the opportunity for faculty members to highlight program resources such as parental support and contingencies to support fellows during challenging times.

The bias toward personalized family-oriented questions toward females does call for attention toward mitigation strategies. This includes the use of structured behavioral interviews with scenario-based questions to assess intangible traits such as motivation or integrity. This has been increasingly adopted and shown to be less susceptible to bias compared to unstructured interviews among pediatric emergency fellowship candidates.[4] Another strategy that can be used adjunctively includes Multiple Mini Interviews, which has previously been shown to have high between-school and within-school reliability for medical school interviews.[5] In addition, use of Multiple Mini Interviews has the potential benefit of also diversifying the interviewer panel, which may further mitigate gender bias.

Limitations of our study include the presence of selection bias due to the voluntary nature of the survey and the lack of nonresponder demographics. Furthermore, the small sample size, low response rate, and unadjusted estimates are vulnerable to confounders. Hence, the results of our study should be interpreted with caution.

10. Sex-Specific Prognosis of Left Ventricular Size and Function Following Repair of Degenerative Mitral Regurgitation

Background

Prior studies have demonstrated worse long-term outcomes for women after surgery for severe mitral regurgitation (MR). The current Class I indications for surgery for severe degenerative MR use cutoffs of left ventricular end-systolic dimension (LVESD) and left ventricular ejection fraction (EF) that do not account for known sex-related differences.

Objectives

The primary objective of this study was to assess long-term mortality following mitral valve repair in women compared with men on the basis of preoperative left ventricular systolic dimensions and EF.

Methods

Consecutive patients who underwent isolated mitral valve repair for degenerative MR at a single institution between 1994 and 2016 were screened. Adjusted HRs for all-cause mortality were compared according to baseline LVESD, LVESD indexed to body surface area (LVESDi), and EF for men and women.

Results

Among 4,589 patients, 1,825 were women (40%), and after a median follow-up period of 7.2 years, 344 patients (7.5%) had died. The risk for mortality for women increased from the baseline hazard at an LVESD of 3.6 cm, whereas an inflection point for increased risk with LVESD was not evident in men. Regarding LVESDi, the risk for women increased at 1.8 cm/m^2 compared with 2.1 cm/m^2 in men. For EF, women and men had a similar inflection point (58%); however, mortality was higher for women as EF decreased.

Conclusions

After mitral valve repair, women have a higher risk for all-cause mortality at lower LVESD and LVESDi and higher EF. These results support consideration of sex-specific thresholds for LVESDi in surgical decision making for patients with severe MR.

11. **Uncovering Sex Differences in Type 2 Myocardial Infarction: Is Coronary Anatomy Enough?**

Introduction

Type 2 myocardial infarction (MI) is a clinical syndrome characterized by myocardial injury that occurs in the setting of an imbalance in myocardial blood supply and demand, in the absence of plaque disruption or atherothrombosis. Since the universal definition of MI first introduced subtypes in 2007, it has become apparent that type 2 MI is underappreciated, more common than type 1 MI, and associated with substantial morbidity and mortality.[1,2] When compared to individuals with type 1 MI, those with type 2 MI tend to be older, are more likely to be female, and have a higher prevalence of cardiovascular comorbidities, such as heart failure and atrial fibrillation.[2] Yet unlike type 1 MI, for which pathophysiology is known and effective treatments are available, coronary mechanisms of type 2 MI have not been systematically elucidated. In a prior study of coronary computed tomography angiography (CCTA) in patients with type 2 MI vs type 1 MI, those with type 2 MI had smaller total, noncalcified, and low-attenuation plaque burdens than those with type 1 MI.[3] However, among patients with type 2 MI, sex-specific differences in clinical presentation and mechanism of MI have not been defined. Unfortunately, due to the deficiencies in our understanding of the pathogenesis of type 2 MI, few targeted therapies have been tested. Instead, supportive care addressing the provoking conditions of type 2 MI and management of traditional cardiovascular risk factors have remained the mainstay of treatment for type 2 MI.

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coronary anatomy among 25 males and 25 females with adjudicated type 2 MI.[5] All participants underwent CCTA during the index hospitalization for MI. Female participants with type 2 MI enrolled in the current study were significantly older than the corresponding males. Peak troponin levels were modest in both sexes (median hs-cTnT of 61 in females and 109 in males), and most participants had electrocardiogram changes or regional wall motion abnormalities by echocardiography, with or without symptoms, to fulfill the Universal Definition of MI criteria. Provoking conditions were heterogenous, and in this small cohort, cases of hypoxemic respiratory failure were numerically higher among males, while tachyarrhythmias, hypertensive urgency, and bleeding occurred in greater numbers among females. At the time of presentation, electrocardiographic ST-segment depressions were more often observed in females, while T-wave inversions were more common in males. Despite this, CCTA revealed no differences in coronary artery calcium scores by sex, and in both males and females with type 2 MI, nonobstructive coronary atherosclerosis was widely prevalent. No differences in calcified and noncalcified plaque volumes were observed in males and females. Women had lower levels of low-attenuation plaque volume, although the clinical relevance of this finding is uncertain. Perhaps most importantly, CCTA-defined obstructive coronary artery disease (CAD), defined by diameter stenosis, or hemodynamically significant lesions, assessed by FFR_{CT} ≥0.80, were identified in only a quarter of males and females with type 2 MI, with no differences by sex.

The authors should be commended for conducting a prospective imaging study of males and females with type 2 MI. Although few sex-specific differences were identified, the findings provide incremental insights to our understanding of the clinical characteristics of type 2 MI. Surprisingly, obstructive coronary artery disease was present in less than one- third of cases in both males and females, raising substantial questions as to the mechanism of ischemic imbalances in patients in the cohort who did not have obstructive or functionally significant CAD. Unfortunately, coronary spasm testing was not performed, and spasm is well recognized as a mechanism for

MI with nonobstructive coronary arteries.[6] Disorders of the microcirculation, comprised of arterioles and capillaries that cannot be visualized by CCTA, might also provoke or exacerbate imbalances in supply and demand during hemodynamic perturbations and cause type 2 MI. Without assessments for coronary spasm and microvascular dysfunction, mechanisms of type 2 MI cannot be adequately explained by plaque burden in many cases. There are other more minor limitations; coronary calcium was prevalent in this cohort, and calcium may impact the accuracy of coronary diameter assessments by CCTA and CT_{FFR}. Notably, the sample size was small and may have conferred insufficient statistical power to identify clinically meaningful sex differences in patient characteristics. Furthermore, the study enrolled a heterogenous cohort with multiple provoking causes of type 2 MI that were not matched by sex, potentially confounding sex-specific comparisons. Finally, a handful of patients with heart failure, in which the diagnosis of type MI can be challenging to adjudicate given the overlap of signs and symptoms of ischemia and volume overload, were included in the cohort.

Ultimately, this small single-center study highlights that remarkably few patients with type 2 MI have obstructive CAD, and this proportion did not differ by sex. Sex differences in plaque characteristics were modest and of uncertain clinical significance. Additional efforts are needed to understand mechanisms of type 2 MI and sex differences relevant to diagnosis and management. Larger studies incorporating coronary functional assessments in addition to coronary anatomy may be required to understand the pathophysiology of this complex and challenging MI subtype.

12. Cardio-Obstetrics Team-Based Management of a Pregnant Patient With Severe Bioprosthetic Aortic Valve Disease

Abstract

A 38-year-old pregnant patient was managed by the cardio-obstetrics multidisciplinary team for severe degenerative bioprosthetic aortic valve

failure. She was medically managed utilizing echocardiogram and brain natriuretic peptide until she demonstrated worsening heart failure. A valve and cardio-obstetrics team evaluation led to valve-in-valve transcatheter aortic valve replacement at 30 weeks' gestation.

Case Presentation

The patient was a 38-year-old G1P000 woman with bicuspid aortic valve disease who 5 years prior to presentation underwent surgery for mixed aortic valvular disease and ascending aortic dilation of 5.2 cm. She received a #23 St. Jude Medical Trifecta stented bioprosthetic graft with end-to-end anastomosis 8-mm Terumo Gelweave Dacron graft. Four years after her surgery, she had issues with swelling and dyspnea. Transthoracic echocardiography (TTE) demonstrated normal left ventricular ejection fraction (LVEF), with a mean gradient across her bioprosthetic aortic valve replacement (AVR) of 22 mm Hg. A year later, she was diagnosed with first-trimester pregnancy. TTE at that time demonstrated an LVEF of 65% and a mean AVR gradient of 33 mm Hg. She was referred to a cardio-obstetrics program at 16 weeks' gestation. TTE demonstrated an LVEF of 70% and mean AVR gradient of 46 mm Hg, with a dimensionless index of 0.28 consistent with moderate-severe stenosis (**Figures 1** and **2**, **Videos 1** and **2**). Her brain natriuretic peptide (BNP) was 106 pg/mL. She was doing well with no cardiac symptoms. Due to her valvular disease and aortopathy, she was classified as modified World Health Organization classification (mWHO) III.

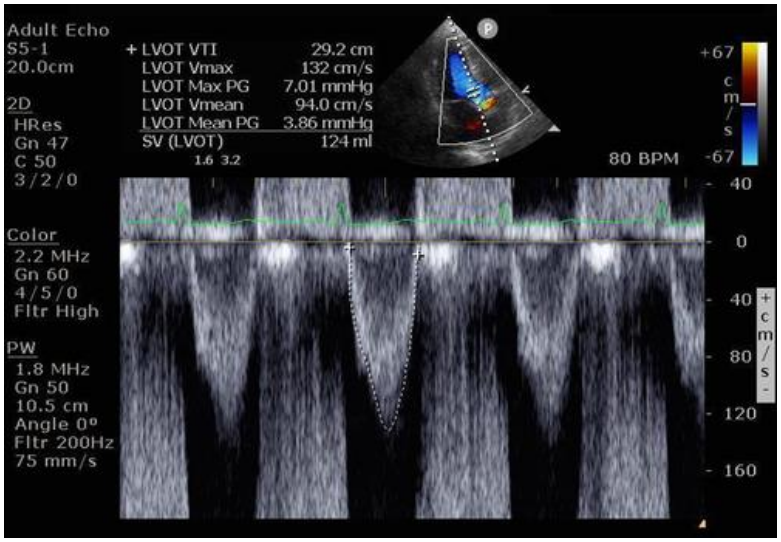

Figure 1

Spectral Doppler Bioprosthetic Aortic Valve Replacement LVOT VTI, Early Second Trimester

The left ventricular outflow tract (LVOT) velocity time integral (VTI) was 29, spectral Doppler aortic valve early second trimester. VTI was 105, dimensionless index was 0.28, and mean aortic valve replacement gradient was 46.4 mm Hg, indicating moderate stenosis. PG = pressure gradient; PW = pulsed wave Doppler; SV = stroke volume; Vmax = peak velocity; Vmean = mean velocity.

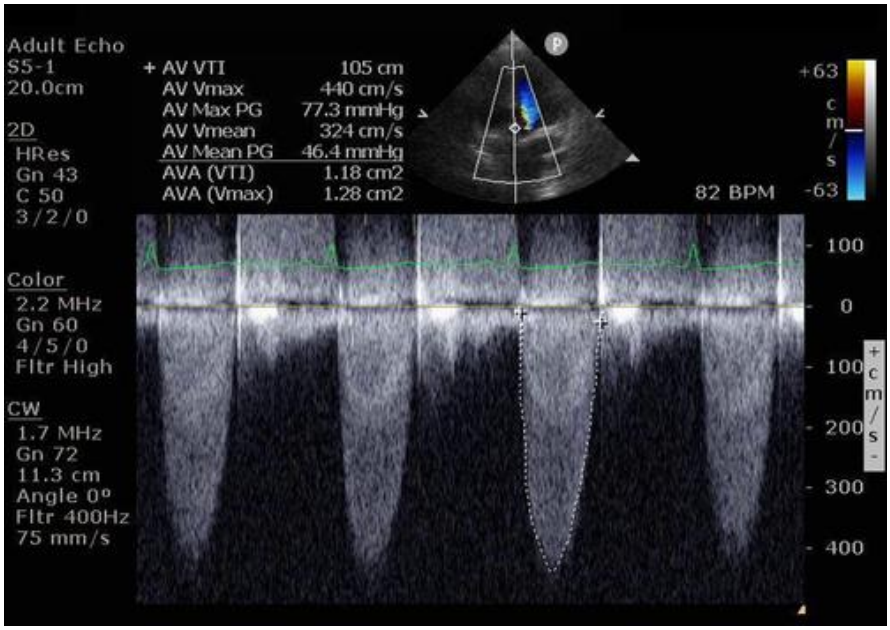

Figure 2

Spectral Doppler Bioprosthetic Aortic Valve Replacement Aortic VTI, Early Second Trimester

The LVOT VTI was 29, spectral Doppler Aortic valve early second trimester. VTI was 105, dimensionless index was 0.28, and mean aortic valve (AV) replacement gradient was 46.4 mm Hg, indicating moderate stenosis. AVA = aortic valve area; CW = continuous wave Doppler; other abbreviations as in **Figure 1**.

Learning Objectives

- To be able to demonstrate the benefit of multidisciplinary management of pregnant patients with cardiac valvular disease utilizing risk stratification, imaging, and cardiac biomarkers.
- To characterize the risk associated with valvular disease in pregnancy and identify patients for whom intervention may improve perinatal outcomes.

She started to have mild heart failure symptoms in her second trimester but was managed with low-dose oral furosemide and monthly TTE as an outpatient. TTE mid second trimester had an ejection fraction of 73%, mean AVR gradient of 67 mm Hg, moderate-to-severe aortic regurgitation, and pressure half time 148 ms (**Figures 3** and **4**, **Video 3**). Due to increasing symptoms and near severe aortic regurgitation, valve team evaluation was undertaken. Transcatheter aortic valve replacement (TAVR) computed tomography (CT) to evaluate for valve-in-valve TAVR was completed. The CT scan demonstrated degeneration of the AVR leading to incomplete closure as the cause of her stenosis and regurgitation. The valve and cardio-obstetrics program teams deemed her suitable to proceed with valve-in-valve TAVR if worsening heart failure refractory to medical management (**Figure 5**, **Video 4**). Monthly evaluation for ongoing severe AVR stenosis and regurgitation was performed. Early in the third trimester, her BNP increased from 200 to 459

pg/mL, and she had worsening lower extremity edema leading to increase in furosemide.

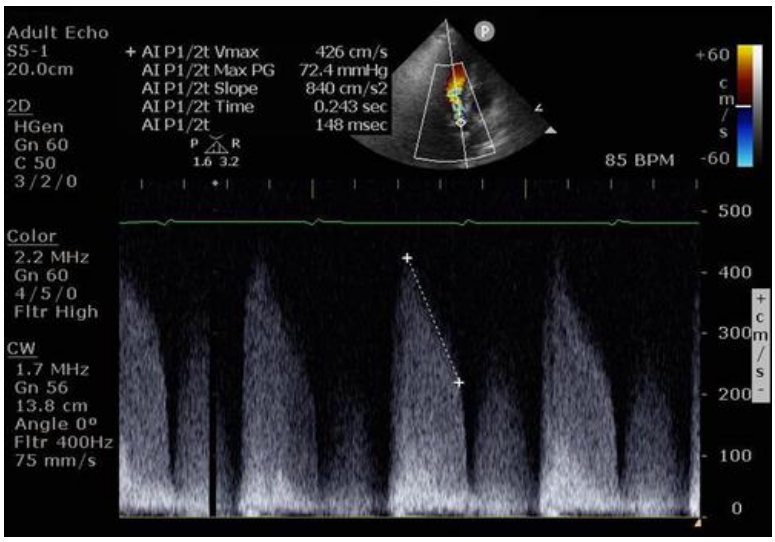

Figure 3

Spectral Doppler Bioprosthetic AV Replacement Aortic Regurgitation, Late Second Trimester

Pressure half time was 148 ms, mean AV replacement gradient was 67 mm Hg, and there was severe stenosis and regurgitation. Abbreviations as in **Figures 1** and **2**.

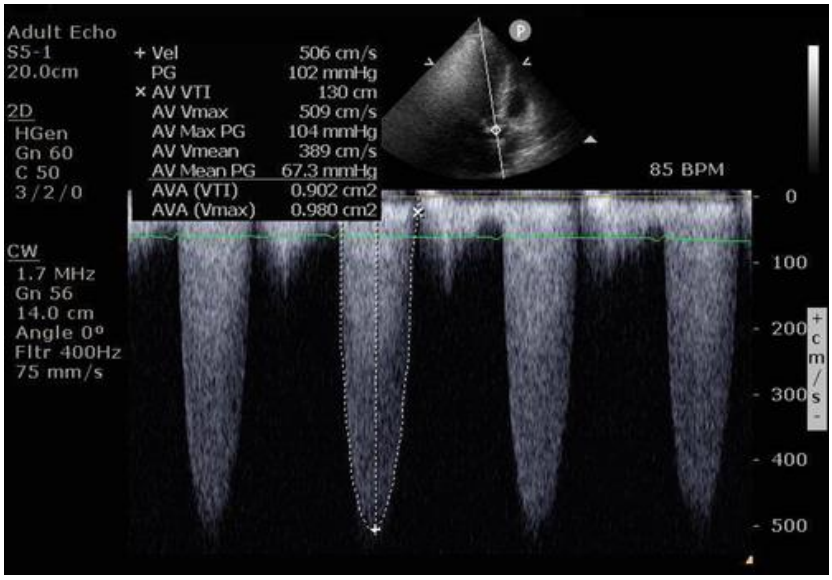

Figure 4

Spectral Doppler Bioprosthetic AV Replacement Aortic Stenosis, Late Second Trimester

Pressure half time was 148 ms, mean AV replacement gradient was 67 mm Hg, and there was severe stenosis and regurgitation. Vel = velocity; other abbreviations as in **Figures 1** and **2**.

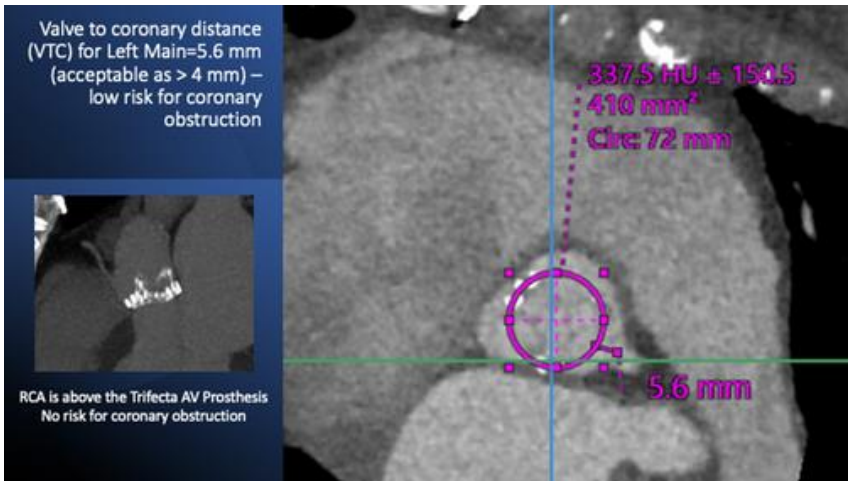

Figure 5

Dose Reduced TAVR CT to Evaluate Size and Coronary Height for Valve in Valve TAVR

Dose-reduced computed tomography transcatheter aortic valve replacement for valve size and coronary distance for valve-in-valve planning within degenerated bioprosthetic aortic valve replacement. Coronary height was acceptable with no risk for coronary obstruction, valve circumference of 72 mm acceptable for a 26 mm Medtronic CoreValve Evolut. RCA = right coronary artery.

At 30 weeks' gestation, she was admitted for worsening heart failure and shortness of breath, with BNP >1000 pg/mL. She was diuresed with intravenous furosemide but had worsening symptoms. From a fetal standpoint, there was appropriate fetal growth in the 56th percentile for gestational age and normal amniotic fluid volume. She had continued worsening heart failure not responding to intravenous furosemide. She was reclassified as mWHO IV and considered high maternal risk. Due to severe

clinical decompensation, she underwent urgent valve-in-valve TAVR for severe bioprosthetic AVR regurgitation.

Both the cardio-obstetrics program team and the valve team managed the patient in preparation for TAVR at 30 weeks and 4 days' gestation. The patient was intubated intraoperatively for transesophageal echocardiography (TEE) guidance. A perinatologist was present during her procedure in case urgent delivery was indicated for fetal distress. She had prophylactic emergency vascular access placed prior to anesthesia induction in case she decompensated. Invasive hemodynamics initially were left ventricular systolic pressure 220 mm Hg, end-diastolic pressure 58 mm Hg, and aortic pressure 148/90 mm Hg. After deployment of a 26-mm Medtronic CoreValve Evolut bioprosthesis TAVR, hemodynamics showed left ventricular systolic pressure 100 mm Hg, end-diastolic pressure 20 mm Hg, aortic pressure 90/60 mm Hg, and mean gradient across the aortic valve 8 mm Hg (**Videos 5 to 10**). No complications occurred. She was extubated same day, further diuresed, and discharged home after 9 days. She was seen back in the cardio-obstetrics program clinic and closely followed post valve-in-valve TAVR. Her mWHO score dropped at time of delivery to II or III. She underwent a term induction of labor at 37 weeks and 4 days' gestation and had a successful vaginal delivery of a healthy female infant. Her postpartum course was uncomplicated.

Question 1: Describe a multidisciplinary cardio-obstetrics program?

A cardio-obstetrics program involves multidisciplinary management of pregnant patients. Patients are evaluated in the preconception period to assess risk for pregnancy, decrease cardiometabolic risk factors, as well as evaluating and substituting teratogenic medications. Patients are then managed through pregnancy with follow-up based on cardiac risk scoring schema. Cardio-obstetrics program meetings are held with the multidisciplinary team in order to develop delivery plans prior to 28 weeks' gestation. The team is made up of cardiologists with expertise in cardio-obstetrics, perinatologists, electrophysiologists, obstetrician-gynecologists,

pharmacists, social workers, obstetric anesthesiologists, cardiac anesthesiologists, cardiothoracic surgeons, neonatologists, hospitalists, and nurse coordinators. Team-based management of pregnant patients is critical to prevent maternal morbidity and mortality.[1,2] cardio-obstetrics program clinics are associated with decreased adverse cardiac complications in pregnancy.[1]

Question 2: How does mWHO risk stratification help manage patients in cardio-obstetrics program?

Several risk stratification models exist, including the CARPREG II (Canadian Cardiac Disease in Pregnancy) expanded risk score and the mWHO classification. Data demonstrate that risk stratification can predict not only pregnancy-associated adverse outcomes, but also long-term cardiac outcomes in the highest risk categories. The risk stratification schema also predicts fetal outcomes. Utilizing mWHO criteria predicts which patients can be managed and delivered at local hospitals vs those who require close monitoring and intervention during pregnancy at expert centers. For pregnant patients at the highest risk, cardio-obstetrics program will monitor serially, recommend changes to delivery location and mode of delivery, and provide other considerations for the delivering obstetric team.[3-5]

Question 3: How does valvular heart disease impact risk during pregnancy?

Valvular heart disease in pregnancy is linked to adverse outcomes. In pregnant patients with both mechanical heart valves and bioprosthetic heart valves, there is an increase in major adverse cardiac events, hypertensive disorders of pregnancy, and ante/postpartum hemorrhage, as well as an increase in duration of hospitalization and cost. Fetal outcomes, including stillbirth, are also increased. There is no significant difference in maternal outcomes between mechanical and bioprosthetic heart valves.[6] Invasive interventions may be needed in severe hemodynamic deterioration of valvular disease. Catheter-based interventions are an alternative to surgery during

pregnancy. Patients who need catheter-based intervention should be evaluated and managed in a multidisciplinary fashion. Procedures should be carried out at experienced centers. To date, valve-in-valve TAVR for bioprosthetic degeneration in pregnancy has been completed in a few cases and limited outcome information is available, but there appears to be short-term safety and efficacy of this intervention.[7]

Question 4: Does BNP aid in the management of pregnant patients?

Hemodynamic changes in pregnancy may lead to maladaptation in pregnant patients with cardiac disease or with an underlying susceptibility to cardiac decompensation. N-terminal pro–B-type natriuretic peptide (NT-proBNP) and BNP are released in cardiomyocyte stretch, myocardial dysfunction, and increased circulating volume. NT-proBNP and BNP are the gold standard in biomarker evaluation for heart failure. In healthy pregnancy with no cardiac dysfunction, NT-proBNP and BNP are stable through all trimesters and postpartum. Both retain their negative predictive value to exclude heart failure in pregnancy. NT-proBNP and BNP can be followed through pregnancy in patients with cardiac lesions at increased risk for heart failure, pre-existing cardiomyopathy, and maternal congenital heart disease. As they should remain stable through trimesters, a significant increase may signal worsening heart failure.

NT-proBNP and BNP increase in patients with preeclampsia. Higher concentrations are seen in early onset and severe preeclampsia. In evaluation of peripartum cardiomyopathy, NT-proBNP and BNP help with diagnosis, and higher levels are associated with worse prognosis. During pregnancy, measurements of NT-proBNP and BNP with signs and symptoms of heart failure may help guide management.[8]

Question 5: What are factors to consider when imaging the pregnant patient?

TTE is the mainstay for evaluating cardiac conditions in the pregnant patient. The American College of Obstetrics and Gynecology recommends that TTE be

performed in all pregnant women with any cardiac diagnosis. Serial evaluation is recommended for valvular and congenital disorders. TTE is considered safe for both the pregnant patient and fetus. TEE in the pregnant patient may have increased risk of emesis and aspiration due to decreased gastric motility, increased relaxation of the lower esophageal sphincter, and increased intra-abdominal pressure. After 18 weeks, pregnant patients are considered "full stomach." Risk and benefits of a TEE must be weighed. Endotracheal intubation is often recommended for TEE after 18 weeks due to the increased risk for aspiration. Fetal considerations for the administration of anesthesia for TEE include fetal hypoxia, possible fetal sedation or distress, and miscarriage/preterm birth; however, routine anesthetics are not teratogenic. Anesthesia/TEE should be pursued if the study alters outcome. Maternal and fetal monitoring should be considered in all procedures after fetal viability or gestational age >22 to 24 weeks, with plans in place for delivery if fetal distress is encountered. CT scanning leads to fetal exposure of ionizing radiation. Doses typically used in clinical practice are well below the threshold for fetal anomalies, intellectual disability, or childhood leukemia.[9] Fetal exposure to radiation should be minimized and appropriate shielding should be used. Shared decision for both CT scanning and TEE should be undertaken. In the setting of management of valve in valve, there is limited utility for 2-dimensional/3-dimensional TEE for valve sizing compared with CT. Undersizing TAVR in pregnancy may lead to worse outcomes; thus, CT scanning may be needed.[10,11]

13. **Infertility Tied to Poorer Cardiovascular Health in Women**

A history of female infertility may serve as a marker for cardiovascular health (CVH) later in life, according to a study published online Jan. 5 in JAMA Network Open.

Amy R. Nichols, Ph.D., R.D., from Harvard University in Boston, and colleagues evaluated the association between infertility history with CVH at

midlife (approximately age 50 years) among parous individuals. The analysis included 468 participants followed for approximately 18 years.

The researchers found that at midlife, the estimated overall American Heart Association Life's Essential 8 score, a construct for ranking CVH in behavioral and biomedical domains, was 2.94 points lower, the biomedical score was 4.07 points lower, and the blood subdomain score was 5.98 points lower among those with versus without a history of infertility. There was also a trend toward a lower point estimate for the behavioral domain score ($\beta = -1.81$).

"This cohort study of parous individuals found evidence for an association between a history of infertility and lower overall and biomedical CVH scores," the authors write. "Our results provide additional weight to evidence suggesting inclusion of infertility history in assessing risk among female patients and demonstrate the importance of early identification and invocation of ongoing cardiovascular preventive strategies."

14. Gender Differences in the Cardiology Fellowship Interview Experience

Cardiology is known for its male predominance and challenging work-life balance. Survey data have indicated that female cardiologists are less likely to have children, more likely to be single, and require childcare help than males.[1] In order to mitigate gender disparities within residency and fellowship interviews, the National Resident Match Program code of conduct strongly discourages questions targeted toward individual characteristics and instead advises focusing on personal interests and program compatibility.[2] In this study, we sought to examine the impact of gender on the interview experience among cardiology fellows across the United States.

We conducted a cross-sectional 13-question survey of cardiology fellows in 2022. The survey was created using Google Forms, and the link was sent to cardiology fellowship program coordinators and subsequently forwarded to all interviewees to be completed anonymously. Two reminder email letters were

sent until the closure of the survey. The questions included demographic characteristics and social questions that might be asked during the interview process. Pearson chi-square tests were used to analyze the differences between responses provided by males and females.

Five hundred surveys were emailed, and 77 responses were received. Fifty-two males (67.5%) and 25 females (32.4%) completed the survey. Baseline demographics were similar between males and females; majority of the participants were between 30 and 45 years of age (86% vs 68%), native English speakers (69% vs 72%), American medical school graduates (65% vs 72%), and from university programs (46% vs 48%). Majority of the male and female participants were of Caucasian (36% vs 44%) and Asian (32% vs 36%) descent. We found that females were more frequently asked about their relationship status, plans for childbearing, and partner support during the fellowship with a statistically significant P value (**Figure 1**).

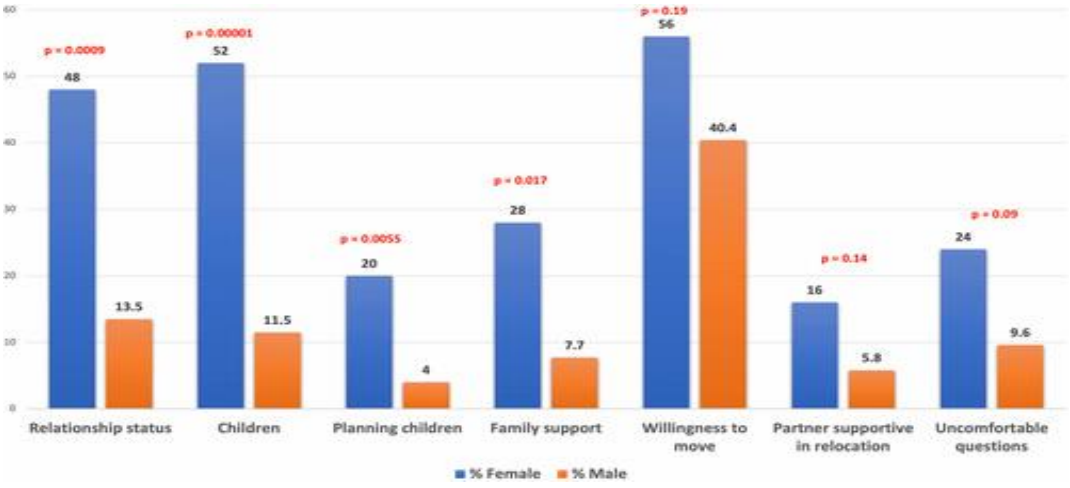

Figure 1

Graphical Representation of Survey Responses Between Males and Females

The presence of personalized family-oriented questions among both males and females signals the importance of work-life balance on the overall well-being of the candidate. Work-life balance has been conceptualized as having multiple domains including time management, fulfillment, and stress

relief.[3] Directed questioning along those domains may provide better insight into a candidate's ability to navigate work-life balance. In addition, this also prompts the opportunity for faculty members to highlight program resources such as parental support and contingencies to support fellows during challenging times.

The bias toward personalized family-oriented questions toward females does call for attention toward mitigation strategies. This includes the use of structured behavioral interviews with scenario-based questions to assess intangible traits such as motivation or integrity. This has been increasingly adopted and shown to be less susceptible to bias compared to unstructured interviews among pediatric emergency fellowship candidates.[4] Another strategy that can be used adjunctively includes Multiple Mini Interviews, which has previously been shown to have high between-school and within-school reliability for medical school interviews.[5] In addition, use of Multiple Mini Interviews has the potential benefit of also diversifying the interviewer panel, which may further mitigate gender bias.

Limitations of our study include the presence of selection bias due to the voluntary nature of the survey and the lack of nonresponder demographics. Furthermore, the small sample size, low response rate, and unadjusted estimates are vulnerable to confounders. Hence, the results of our study should be interpreted with caution.

15. **Prolactin Inhibition to Treat Postpartum Arrhythmic Storm**

Postpartum electrical storm due to torsade de pointes is a rare but life-threatening condition. The uniqueness of this case lies in the use of cabergoline to suppress postpartum ventricular arrhythmias in absence of heart disease. Timely multidisciplinary management is crucial to achieve final diagnosis, deliver proper treatment and improve prognosis.

Introduction

A 36-year-old woman was admitted to the hospital because of unexplained recurrent syncope without prodromal symptoms. Five days prior, she had undergone a successful delivery and was breastfeeding. On admission, her vital signs were normal, and she was well perfused, with no peripheral edema. A 12-lead electrocardiogram (ECG) showed sinus rhythm with normal QTc segment duration (Bazett formula) but frequent monomorphic short coupled premature ventricular contractions (PVCs) (**Figure 1A**). The PVCs had a left bundle branch block morphology with left superior axis, potentially from the right ventricular apex. During observation, the woman went into cardiac arrest caused by to torsade de pointes (TdP) (**Figures 1B** and **1C**).

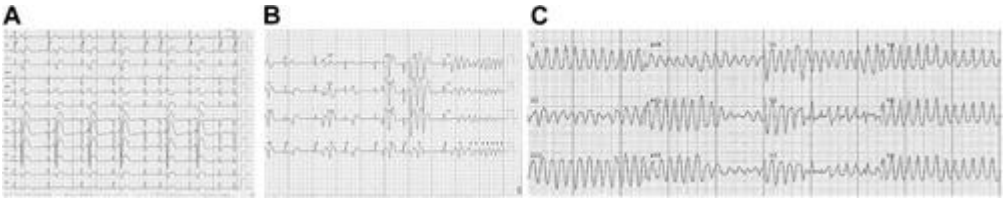

Figure 1

12-Lead Electrocardiogram

(A) Frequent premature monomorphic short-coupled premature ventricular contractions; the coupling interval was 280 msec. (B, C) Torsade de pointes episode, with typical gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line.

Learning Objectives

- To learn management of postpartum arrhythmic events in absence of heart disease.
- To understand the TdP treatment with cabergoline in postpartum setting.

Medical History

The patient was a primipara, and the pregnancy was uneventful. There was a family history of sudden cardiac death, with the patient's mother dying unexpectedly at age 34 years. The patient was taking no medication at home.

Differential Diagnosis

The differential diagnosis included peripartum cardiomyopathy, spontaneous coronary dissection, and type 2 long QT syndrome (LQT2).

Investigations

Laboratory tests excluded electrolyte, acid-base, and thyroid disorders. Her high-sensitivity troponin-T level was normal, as was a fast transthoracic echocardiogram study. Emergency angiography showed patent, healthy coronary arteries with no signs of spontaneous coronary dissection. A right ventricular biopsy excluded inflammatory and infiltrative disorders. Cardiac magnetic resonance showed normal biventricular function, volumes, and wall thickness (**Figure 2**) without wall edema or late gadolinium enhancement. A whole-body computed tomography scan was also normal.

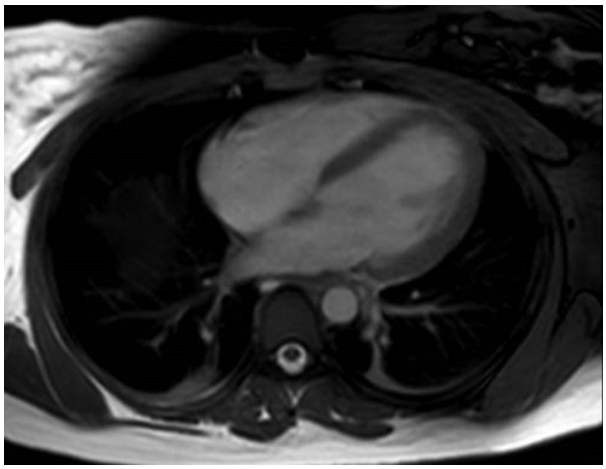

Figure 2

Cardiac Magnetic Resonance

Image showing normal left ventricular systolic fraction.

Management

The cardiac arrest was treated with cardiopulmonary resuscitation (CPR) and a single DC shock. Magnesium sulfate infusion was administered, but the nonsustained TdP persisted. She was transferred to the catheterization laboratory, where she experienced multiple recurrent TdP episodes with cardiac arrest (>50 episodes) requiring prolonged CPR, repeated DC shocks, and orotracheal intubation under general anesthesia. Intravenous amiodarone, lidocaine, and metoprolol were used without success, and overdrive pacing through a temporary pacemaker failed to prevent electrical storm (ES) episodes. An intra-aortic balloon pump was placed to improve her hemodynamic status. The Impella left ventricular assist device was not used because of potentially marked ventricular arrhythmic susceptibility triggered by contact between catheter and endocardium. In addition, complete biventricular hemodynamic support, needed in case of protracted circulatory arrest, was not available. A percutaneous stellate ganglion block was also performed but proved ineffective. After prolonged CPR, during a phase of relative stability, the patient was transferred to a tertiary heart center. She underwent an electrophysiological study with biventricular electroanatomic mapping. A drug test with ajmaline was also performed, which showed no alterations to suggest Na channel modification. A focus of triggered activity was identified in the right septal apical area and was successfully treated by transcatheter radiofrequency ablation. However, 2 days after the procedure, the patient experienced further TdP relapses. Despite persistently normal QTc intervals, LQT2 was suspected. Accordingly, propranolol was tested[1] but was discontinued after being poorly tolerated. A genetic test was also performed, with negative results. Afterward, intravenous verapamil, flecainide, and isoproterenol were also proved ineffective in suppressing the arrhythmias. In view of the temporal association between her postpartum state and the onset of ES, a cause-and-effect association was suspected. Therefore, in agreement with the gynecologists, cabergoline was used to inhibit lactation, resulting in successful suppression of the ES. An implantable subcutaneous cardiac defibrillator was placed for secondary prevention, and the patient was discharged in good clinical condition.

Discussion

This was a case of ES caused by recurrent postpartum TdP in a patient without structural heart disease. It is a medical emergency that can frequently lead to hemodynamic instability and tends to have a poor prognosis.[2,3] Treatment is not standardized, and there is substantial heterogeneity among centers.[3] The underlying causes should be investigated to provide targeted treatment, but this is not always possible, especially while conditions are acute and unstable. Owing to the prominent role of increased adrenergic tone, intravenous β-blockers alone or combined with amiodarone are the most common first-line treatment options.[2,3] Selected patients may benefit from autonomic modulation via percutaneous stellate ganglion block or sympathetic denervation.[2] Sedation and general anesthesia play a crucial role in supporting vital functions and decreasing adrenergic stress. In cases of TdP, intravenous magnesium is an effective treatment even in the absence of hypomagnesemia, and in refractory cases, particularly if associated with bradycardia, the arrhythmia can be suppressed by increasing the underlying heart rate using isoprenaline or transvenous pacing.[2] When ES persists unresponsive to medical treatment, catheter ablation should be considered. Currently, urgent catheter ablation is a Class I, Level of Evidence: B recommendation;[2] however, in the vast majority of centers, this treatment is available only during the day and on workdays.[3] Early referral to centers that can guarantee advanced circulatory support (eg, venoarterial extracorporeal membrane oxygenation) and fast access to ventricular ablation is of paramount importance, as is identifying the underlying cause. However, the causes of ES are often not fully understood, especially during peripartum.[4] In general, during pregnancy ES is typically associated with hemodynamic decompensation of a pre-existing structural heart disease (eg, cardiomyopathy, valvular or congenital heart disease, pulmonary hypertension) or is due to specific pathological entities that typically occur at the end of pregnancy or in the following months.[5] By contrast, new-onset ES is extremely rare in the absence of structural heart disease. Baseline 12-lead ECG characteristics have a high diagnostic yield for underlying arrhythmic

disorders (eg, Brugada and early repolarization pattern, catecholaminergic polymorphic ventricular tachycardia, short or long QT syndrome). However, as shown in our case, the ECG can be completely normal. Despite ES being extremely rare in the peripartum, more benign rhythm disorders (eg, PCVs) are quite common. The main proarrhythmic mechanisms in peripartum include[5,6]:

1. increased heart rate
2. increased blood volume, resulting in cardiac chamber enlargement with a risk of re-entrant phenomena or stretch-sensitive ion-channel activation
3. increased sympathetic activity, which may contribute to abnormal automaticity, reentry, or triggered activity
4. rapid changes in hormone levels during pregnancy or after delivery

Previous studies have demonstrated how decreased progesterone levels may contribute to heightened arrhythmogenic risk during the postpartum period and how oxytocin prolongs the QT interval even in healthy subjects.[6,7] In fact, progesterone is able to modify membrane potential response to Ca^{2+} oscillations and reduce the likelihood of triggered activity.[7] Furthermore, both oxytocin and prolactin have been proved to affect repolarization and contribute to an increased propensity for arrhythmic events in LQT2.[7] During pregnancy, circulating prolactin rises progressively, and its action is inhibited by high plasma levels of placental estrogen and progesterone. After delivery, there is a drop in these hormones and an increased release of prolactin resulting from the newborn's breastfeeding. In our case, the high prolactin level may have increased ventricular vulnerability with a proarrhythmic effect. This hypothesis derives from these conditions:

1. the inefficacy of standard treatment

2. the temporal relation between the ES onset and breastfeeding
3. the complete cessation of malignant arrhythmic events after use of a prolactin inhibitor

To date, the role of postpartum hormones in triggering ES is not completely understood, and further studies are needed.

Follow-Up

At the 1-year follow-up visit, the patient's progress was uneventful, with the implantable subcutaneous cardiac defibrillator interrogation reporting no syncope, no shocks, or recurrence of ventricular arrhythmic events.

Conclusions

Life-threatening arrhythmic events occurring in the peripartum setting may have multiple causes, which must be investigated quickly while making complex treatment choices. A well-established network among centers with different levels of care and a multidisciplinary team approach are key factors in ensuring the best diagnostic and therapeutic options.

16. **Preconception Counseling for a Patient With a Mechanical Tricuspid Valve**

Abstract

A 37-year-old woman with mechanical tricuspid valve thrombosis presented for preconception consultation. Multimodality imaging confirmed a malfunctioning bileaflet mechanical tricuspid valve with both leaflets fixed and open. This case highlights the key discussions held by the multidisciplinary pregnancy heart team.

Case Presentation

A 37-year-old woman presented to the multidisciplinary cardio-obstetrics clinic for preconception consultation. Her medical history included remote intravenous drug use and tricuspid endocarditis, which led to bioprosthetic tricuspid valve replacement (Mosaic #29, Medtronic) at 31 years of age. She had early degeneration of the bioprosthetic valve and subsequently underwent redo sternotomy with mechanical tricuspid valve replacement (On-X, Life Technologies) at 33 years of age. Seven months before the present clinic visit, she conceived a highly desired pregnancy. She had been transitioned from warfarin to low molecular weight heparin 2 months before conception. The patient developed heart failure symptoms around 10 weeks' gestation. A transthoracic echocardiogram revealed an increased gradient of 15/7 mm Hg (peak/mean) across the prosthetic tricuspid valve and mild to moderate tricuspid regurgitation. Subsequent transesophageal echocardiography (TEE) showed a similar transvalvular pressure gradient with suboptimal visualization of the leaflets, and it was attributed to mechanical valve thrombosis. Systemic thrombolytic therapy was avoided because of the pregnancy, and the patient was treated with unfractionated heparin, which was transitioned to warfarin at discharge. Her heart failure symptoms improved with medical management, but she had a miscarriage at 15 weeks' gestation.

Learning Objectives

- To assess and counsel risks of adverse maternal and fetal outcomes for a patient with mechanical tricuspid valve dysfunction.
- To demonstrate multidisciplinary heart team approach in the management of mechanical tricuspid valve thrombosis.

At our clinic visit, the patient expressed a strong desire for another pregnancy. She did not report any heart failure symptoms. Cardiac examination was notable for the absence of audible mechanical valve sounds. Her international normalized ratio was within the therapeutic range (2.5-3.5) on warfarin (55 mg/week). The most recent transthoracic echocardiogram before the visit

showed normal biventricular function and prosthetic tricuspid valve gradient of 19/11 mm Hg (peak/mean).

Question 1: What are maternal and fetal risks related to mechanical prosthetic valves? How should we approach preconception counseling in this patient?

Although our patient was clinically stable, she remained high risk for complications during future pregnancy. The presence of a mechanical tricuspid valve, recent prosthetic valve thrombosis despite therapeutic anticoagulation, and a history of early bioprosthetic valve degeneration all raise the risk for cardiac complications during pregnancy, especially recurrent thrombosis, prosthetic valve dysfunction, and heart failure. In addition, the existing valvular dysfunction may be exacerbated by normal physiologic changes of pregnancy including increased intravascular volume, cardiac output, and hypercoagulability.

Cardiovascular risk assessment scores and classifications such as the modified World Health Organization classification, the ZAHARA (Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking) risk score, and CARPREG (Cardiac Disease in Pregnancy) II all place the presence of a mechanical heart prosthesis in high-risk categories.[1-3] The risk of a maternal adverse cardiovascular event related to mechanical valve prosthesis has been estimated to be 19% to 27% based on the modified World Health Organization classification, >70% based on ZAHARA, and 41% based on the CARPREG II study.[1-3] Moreover, moderate to severe atrioventricular valve dysfunction has the additional risk of adverse maternal cardiac outcomes based on the ZAHARA study.[2] A retrospective study using the National Inpatient Sample found that pregnant individuals with valvular disease had higher odds of adverse obstetrical events such as pre-eclampsia; eclampsia; intrapartum/postpartum hemorrhage; and cardiovascular events including peripartum cardiomyopathy, pulmonary edema, acute ischemic heart disease, and arrhythmias.[4]

We discussed at length her high risk of valve complications during pregnancy. Our final recommendations were to start contraception and address the prosthetic valve dysfunction before planning another pregnancy. Therefore, a multidisciplinary heart team meeting was arranged to discuss her case.

Question 2: What is the differential diagnosis for elevated pressure gradient across the prosthetic valve?

The most common causes of mechanical prosthetic valve dysfunction are valve thrombosis and pannus formation.[5] Differentiating thrombosis from pannus overgrowth can be challenging but essential because some patients may be eligible for thrombolytic therapy in case of acute thrombosis. Other causes of pathologic elevation of pressure gradient across the prosthetic valve include prosthesis-patient mismatch and valvular degeneration in case of a bioprosthetic valve. A mild increase in the pressure gradient across the prosthetic valve may be seen during normal pregnancy when the cardiac output increases. However, concomitant regurgitation or the development of heart failure symptoms should raise concern for prosthetic valve dysfunction.

Question 3: What is the heart team approach in assessing the mechanical tricuspid valve function and need for intervention?

Our initial approach included assessment of the prosthetic valve function using multimodality imaging. The patient underwent TEE (**Video 1**), valve cinefluoroscopy (**Video 2**), and computed tomography angiography (**Video 3**), all of which confirmed a bileaflet mechanical tricuspid valve with both leaflets fixed in a partially open position with no observable movement. The fixed leaflets resulted in moderate tricuspid valve stenosis (mean gradient of 6 mm Hg at a heart rate of 74 beats/min) (**Figure 1**) and moderate to severe regurgitation. In general, a mean gradient ≥5 mm Hg or a valve area ≤1.0 cm^2 are echocardiographic indicators of severe tricuspid valve stenosis.[6] Although there was no obvious thrombus or pannus visualized on TEE, it was thought that thrombosis was the most likely etiology of her valve dysfunction. However, the decision regarding surgical intervention was

unclear in the absence of symptoms. An exercise stress test was pursued for better assessment of her functional capacity and symptomatology. She achieved a peak work level of 13 metabolic equivalents and a maximum heart rate of 157 beats/min (85% of the maximal, age-predicted heart rate) on the treadmill exercise stress test. She did not have any reportable symptoms during the test.

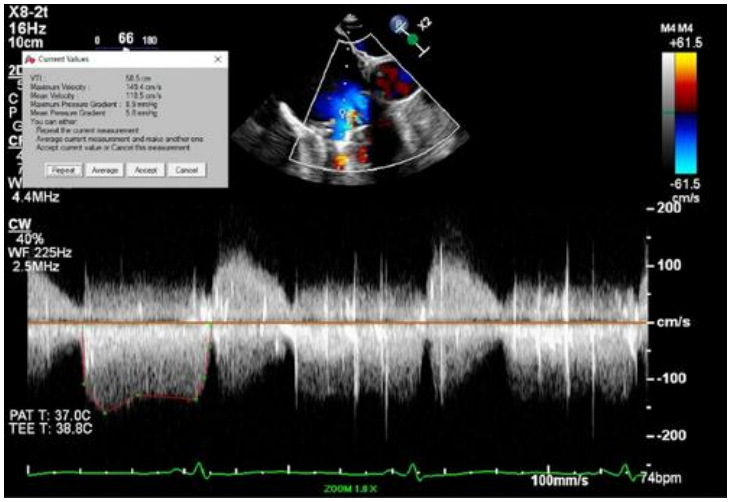

Figure 1

Continuous Doppler Across the Mechanical Tricuspid Valve

The mean pressure gradient across the mechanical tricuspid valve was 5.8 mm Hg at a heart rate of 74 beats/min.

Question 4: How does pregnancy affect the safety of multimodality imaging studies?

Multimodality cardiac imaging plays a critical role in determining the etiology and severity of prosthetic valve dysfunction. Although most imaging modalities are noninvasive and safe, special considerations need to take place when the patient is pregnant. Our team strongly recommended obtaining multimodality imaging studies before considering pregnancy because some imaging modalities may not be suitable during pregnancy because of safety concerns. An increased progesterone level during pregnancy is thought to decrease gastric motility and increase relaxation of the lower esophageal sphincter, which may lead to an increased risk of emesis and aspiration in a

patient with increased intra-abdominal pressure from a gravid uterus.[7] This is an important consideration for sedation before TEE, and many anesthesiologists consider pregnant women's fasting status to be "full stomach" regardless of fasting duration beyond 18 weeks' gestation.[8] According to the American College of Obstetricians and Gynecologists, absolute contraindications to submaximal exercise stress testing in pregnant women include persistent vaginal bleeding, an incompetent cervix, multiple gestation, placenta previa after 26 weeks, preterm labor, premature rupture of membranes, restrictive lung disease, pre-eclampsia/gestational hypertension, and known hemodynamically significant cardiovascular disease.[9] Non–weight-bearing exercise on a recumbent bike is preferred to the treadmill test during pregnancy, particularly in individuals who are unaccustomed to physical exertion or experiencing gait instability.[8] When using cardiac imaging modalities with ionizing radiation, potential fetal radiation exposure needs to be considered, and such risk needs to be weighed against diagnostic benefit.

Question 5: Which intervention was ultimately recommended for this patient?

Although the patient did not experience significant symptoms related to her mechanical tricuspid valve dysfunction, it was thought that her persistent mixed valve disease from chronic thrombosis would not resolve with anticoagulation alone and she would eventually require surgical intervention. Systemic thrombolytic therapy was not thought to be beneficial in this case because of the chronicity of her valve disease (longer than 6 months). Given the patient's advanced maternal age and her strong desire for future pregnancy, the recommendation was made to proceed with redo tricuspid valve replacement with a bioprosthetic valve in order to avoid long-term anticoagulation. The patient underwent successful surgical replacement of the existing mechanical tricuspid valve with a porcine mitral bioprosthetic valve (Mosaic #29). A bovine pericardial valve could not be used because of a history of nickel allergy. Intraoperative visual inspection of the mechanical

prosthetic valve confirmed the presence of organized thrombus obstructing 1 of the 2 leaflets in a fixed position (**Figure 2**).

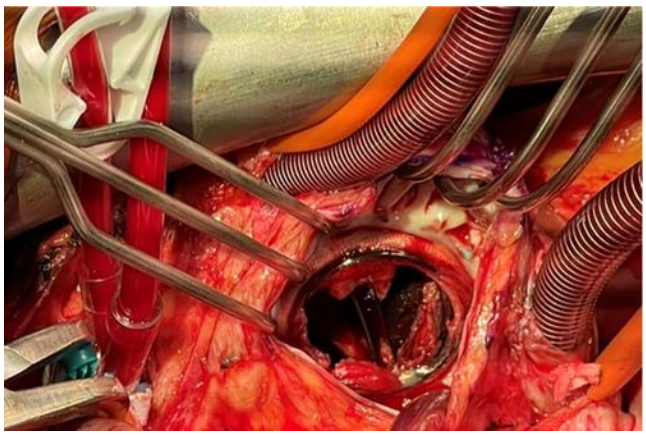

Figure 2

Mechanical Tricuspid Valve With Chronic Thrombosis

Intraoperative visual inspection confirmed an organized thrombus obstructing 1 of the 2 leaflets of the valve.

Conclusions

Our case highlights the importance of working in a multidisciplinary team composed of members from maternal fetal medicine, cardio-obstetrics, advanced cardiac imaging, cardiac surgery, and interventional/structural cardiology when providing preconception counseling for a patient with complex prosthetic valve disease.

17. **Complex Congenital Heart Disease and Congenital Uterine Anomalies Impacting Pregnancy Outcomes**

Introduction

Congenital uterine anomalies (CUAs), also known as müllerian anomalies, are a known risk factor for obstetrical complications such as premature delivery and miscarriage.[1] Complex congenital heart disease (CCHD), such as heterotaxy and single-ventricle disease, is often accompanied by extracardiac manifestations; however, the exact correlation and significance of

genitourinary involvement remain unclear. We present a case series of 3 patients with palliated CCHD who had pregnancies complicated by premature delivery and were subsequently found to have CUAs that may have contributed to their obstetrical complications.

Learning Objectives

- To understand the association of extracardiac anatomical malformations, such as CUAs, in CCHD.
- To appreciate how CUAs may augment obstetrical risk in patients with CCHD.
- To consider screening patients with CCHD who are undergoing prepregnancy counseling for CUAs with pelvic MRI.

Case 1

A 32-year-old G1P0000 woman with a history of congenitally corrected transposition of the great arteries with a restrictive ventricular septal defect and pulmonary valve stenosis status post hemi-Mustard baffle, a Rastelli-type left ventricle-to- aorta tunnel, a bidirectional Glenn procedure, and a right ventricle-to-pulmonary artery 28-mm conduit homograft, type 1 diabetes managed with an insulin pump, and atrial fibrillation status post ablation presented at 35 weeks' gestation with preterm premature rupture of the membranes and preeclampsia with severe features, and ultimately failed induction necessitating emergency cesarean delivery. At the time of delivery, she was found to have a bicornuate uterus. She had an unremarkable postpartum course. She later had 2 further pregnancies; both deliveries were premature but were otherwise uncomplicated.

Case 2

A 27-year-old G2P0010 woman with a history of tricuspid atresia status post lateral tunnel Fontan procedure at age 2 years, coarctation of the aorta status

post- stent placement at age 17 years, atrial septal defect, fenestration closure at age 21 years after a thrombotic stroke, and Fontan-associated liver disease with high-grade fibrosis (F3) presented at 32 weeks' gestation with loss of fetal movement and was found to have nonreassuring fetal heart tones necessitating emergency cesarean delivery. At the time of delivery, she was found to have a bicornuate uterus. The hysterotomy incision inadvertently involved a portion of her abnormal septum and complicated her initial postpartum course with postpartum hemorrhage; however, she ultimately returned to her cardiac baseline.

Case 3

A 24-year-old G3P0020 woman with a history of heterotaxy with asplenia and right atrial appendage isomerism, hypoplastic left heart syndrome, double-outlet right ventricle, and interrupted inferior vena cava status post Kawashima-type Fontan procedure, Fontan-associated liver disease with high-grade fibrosis (F3), and 2 previous miscarriages, presented at 23 weeks' gestation with concern for shortened cervical length and uterine didelphys. She was initially managed expectantly until she went into preterm labor at 28 weeks with concern for footling breech presentation, necessitating emergency cesarean delivery. At the time of delivery, she was found actually to have bicornuate uterus. Her postpartum course was notable for postpartum depression but was otherwise uncomplicated.

Discussion

As has been increasingly recognized, patients with CCHD phenotypes that were previously not survivable into adulthood are now able to undergo a variety of complex palliative surgical procedures that have dramatically improved their survival. With this improvement has come an increasing number of patients with CCHD who desire pregnancy and a search to characterize their risk and likelihood of success so we may best counsel them. Although guidelines are robust with regard to their recommendations for cardiac work-up and treatment, there is little about extracardiac

manifestations that are common with these patients and may affect their ability to both achieve pregnancy and carry it to term.[2,3]

CUAs, also known as müllerian duct anomalies, are a wide spectrum of anatomical malformations of the uterus. The underlying pathophysiology involves disruption of the normal embryologic development of the uterus somewhere in the process of differentiation, migration, unification, and canalization of the müllerian duct system. Although there is no universally accepted classification system for CUAs, the 2021 American Society for Reproductive Medicine classification system is the accepted standard in the United States and divides these anomalies on this embryologic basis while accounting for the wide variety of manifestations (**Figure 1**).[4,5] Each subtype carries different obstetrical considerations (**Table 1**).[1] CUAs are best evaluated by magnetic resonance imaging (MRI) because it can define both external and internal contours of the uterus; however, CUAs are often first suspected on the basis of pelvic ultrasound or, as in 2 of our cases, found at the time of delivery.[6] Furthermore, CUAs may complicate cesarean delivery, thus adding further risk to already complicated deliveries and even damage to an already anatomically malformed uterus, as seen in case 2.

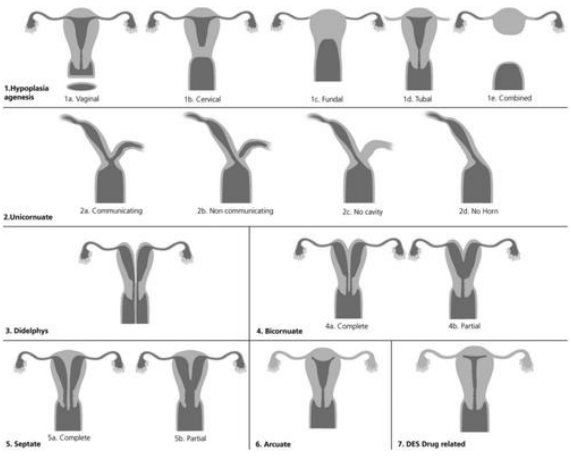

Figure 1

Spectrum of Congenital Uterine Anomalies

Congenital uterine anomalies (CUAs) can be categorized into the following broad categories on the basis of the timing of disruption of normal

embryologic development of the Müllerian ducts. This figure actually simplifies many of the anomalies, which were further delineated in the 2021 American Society for Reproductive Medicine guidelines, as referenced in the text. Reprinted with permission from Behr et al[5]. DES = diethylstilbestrol.

Table 1Obstetrical Complications of Congenital Uterine Anomalies

Area of Embryologic Disruption	Congenital Uterine Anomaly	Obstetrical Complications
Hypoplasia/agenesis	—	Infertility
Unification	Unicornuate	Miscarriage, prematurity, fetal malpresentation, ectopic pregnancy
	Bicornuate	Miscarriage, prematurity, and fetal malpresentation
	Didelphys	Prematurity
Canalization	Septate	Miscarriage, prematurity, and fetal malpresentation
	Arcuate	Second trimester pregnancy loss, fetal malpresentation

The most common association of CUAs is with renal malformations, most commonly unilateral renal agenesis or multicystic dysplastic kidney.[6] Only 1 recent case series has looked specifically at the association between CUAs and CCHD, by presenting 8 patients with a majority single ventricle or transposition patients with unification defects.[7] No larger studies exist that describe the prevalence of CUAs in persons with congenital heart disease, nor are there any studies looking at the compounded obstetrical risk that having both may conditions carry. Although one may hypothesize an association between genetic syndromes and the concomitant presence of CUA and CCHD,

none of our 3 patients had an identified genetic syndrome. It may be reasonable to offer genetic counseling and consider genetic testing for these patients, as noted in the 2018 American Heart Association and American College of Cardiology guideline for management of adults with congenital heart disease, because this may be missed in patients with CCHD where it is not phenotypically apparent.[8]

In the most recent systemic review on pregnancy outcomes in patients with a Fontan circulation, Garcia Ropero et al[9] showed that there was a high incidence of miscarriages, prematurity, and intrauterine growth restriction. These investigators wrote that this is "driven by a combination of factors, including placental insufficiency, intrinsic morphological uterine abnormalities, and adverse hemodynamics related to the Fontan circulation"[9]; however no dedicated studies have looked at the prevalence of CUAs in these patients. Other subtypes of CCHD such as heterotaxy do not have as robust studies on obstetrical outcomes, although similar complications can be expected for similar reasons. In our cases, determining which factors affected their premature deliveries to what extent is difficult given the known association of premature delivery with their forms of CCHD. In all 3 cases, limitations in cardiac output augmentation were compounded by placental abnormalities that have been shown to be associated with CCHD.[10] Furthermore, although CUAs are known risk factors for prematurity and miscarriage, there may also be a yet undefined disruption in postnatal uterine development in patients with prolonged or profound cyanosis that may affect the ability of the uterus to carry pregnancy, as well as increase the risk of complications such as postpartum hemorrhage.

Overall, these cases are hypothesis generating for an underappreciated association between CCHD and CUAs. It may be reasonable to consider uterine imaging for CUAs, ideally with MRI, as part of prepregnancy planning and risk stratification in patients with CCHD who desire pregnancy, especially if there is a history of spontaneous abortions, as was the case with 2 of our patients. Further research is needed to better describe the prevalence of CUAs with CCHD and identify more specific associations that may allow for better

pregnancy counseling as more patients from this group continue to age and become of child-bearing potential.

18. **Sex-Specific Prognosis of Left Ventricular Size and Function Following Repair of Degenerative Mitral Regurgitation**

Background

Prior studies have demonstrated worse long-term outcomes for women after surgery for severe mitral regurgitation (MR). The current Class I indications for surgery for severe degenerative MR use cutoffs of left ventricular end-systolic dimension (LVESD) and left ventricular ejection fraction (EF) that do not account for known sex-related differences.

Objectives

The primary objective of this study was to assess long-term mortality following mitral valve repair in women compared with men on the basis of preoperative left ventricular systolic dimensions and EF.

Methods

Consecutive patients who underwent isolated mitral valve repair for degenerative MR at a single institution between 1994 and 2016 were screened. Adjusted HRs for all-cause mortality were compared according to baseline LVESD, LVESD indexed to body surface area (LVESDi), and EF for men and women.

Results

Among 4,589 patients, 1,825 were women (40%), and after a median follow-up period of 7.2 years, 344 patients (7.5%) had died. The risk for mortality for women increased from the baseline hazard at an LVESD of 3.6 cm, whereas an inflection point for increased risk with LVESD was not evident in men. Regarding LVESDi, the risk for women increased at 1.8 cm/m^2 compared with

2.1 cm/m^2 in men. For EF, women and men had a similar inflection point (58%); however, mortality was higher for women as EF decreased.

Conclusions

After mitral valve repair, women have a higher risk for all-cause mortality at lower LVESD and LVESDi and higher EF. These results support consideration of sex-specific thresholds for LVESDi in surgical decision making for patients with severe MR.

19. Across the Globe, Some Sex Gaps Still Seen in Congestive Heart Failure

Men and women with congestive heart failure (HF) diverge in many ways—in terms of not only the disease itself but also its impact on all-cause mortality. But the sex-related patterns are consistent across countries regardless of economic status, international data from the Global Congestive Heart Failure (G-CHF) registry suggest.

As in prior studies, male patients were more likely than female to get an implantable cardioverter-defibrillator (ICD), report Marjan Walli-Attaei, PhD (Population Health Research Institute and Hamilton Health Sciences, Hamilton, Canada; University of Oxford, England), and colleagues in the Lancet Global Health. But, unlike in earlier data showing acute HF care for women falls short, here management was largely similar irrespective of sex, with no differences in chronic medication use or hospitalization for HF.

Co-author Philip Joseph, MD (Population Health Research Institute and Hamilton Health Sciences), said the G-CHF registry data capture a broad swath of information. “The study is pretty unique because we were able to look at characteristics, management, and outcomes in women compared to men on a more global [scale],” he told TCTMD, noting that there has been some controversy in the literature about the extent of sex-related differences in heart failure.

What the results also highlight, said Joseph, is that any disparities between male and female patients are smaller than those between lower- and higher-income countries. “The biggest gaps that we see from a global heart failure management standpoint . . . are between countries of different income levels,” he noted.

Walli-Attaei et al analyzed data for 23,341 people (60.1% male) enrolled in the G-CHF study across 257 centers in 40 countries over a 4-year period ending in September 2020. Follow-up lasted a mean of 2.6 years.

The mean age was 64 for men and 62 for women. Hypertensive HF was the most common etiology for women, at 25.5%, whereas the most common etiology in men was ischemic HF (45.6%). Women in general had a higher LVEF, with fewer female than male patients having an LVEF of 40% or lower (51.7% vs 66.2%). A third of women had an LVEF of 50% or higher, as compared with 18.6% of men.

Female patients were more likely to have signs and symptoms of congestion (NYHA functional class III or IV: 42.6% vs 37.9%). They also reported lower health-related quality of life.

For the most part, treatments were similar by sex. There were no significant differences in the use of heart failure drugs or cardiac tests. Importantly, though, women were less likely to receive an ICD (8.7% vs 17.2%).

Women and men, after adjusting for potential confounders, were also equally likely to be hospitalized for HF, with 10 admissions per 100 person-years in each group. Across the world, the largest difference was seen in Europe, where 9.4 women and 11.5 men per 100 person-years were hospitalized for heart failure. Hospitalization rates were consistent among countries categorized by economic status and within geographical regions.

There was, however, a gap in all-cause mortality: the incidence of death was 10.8 per 100 person-years in women and 13.5 per 100 person-years in men (adjusted HR 0.79; 95% CI 0.75-0.84). Again, the largest disparity was seen

in Europe, where the per 100 person-year incidence was 7.8 in women and 11.8 in men, and results were similar within geographical regions and within countries of the same income level. Female patients, compared with male, had lower mortality in both high-/upper-middle-income countries (HR 0.81; 95% CI 0.71-0.93) and low-/lower-middle-income countries (HR 0.80; 95% CI 0.69-0.93).

“The paradox of why men have a higher mortality than women despite having less severe symptoms of heart failure, similar or lower age, after adjustment for ejection fraction levels, mostly similar levels of medications, and similar rates of heart failure hospitalization is not clear,” the authors note, urging that there need to be vigorous efforts to both investigate and mitigate whatever is driving the worse survival.

Additionally, Joseph said that the difference in ICD use merits a closer look, given how consistently it’s being seen. A possible explanation is concerns about the possibility of higher complication rates among women versus men receiving ICDs.

The paradox of women having more symptomatic heart failure and men having higher mortality “really needs to be understood, because from a patient perspective both of these are quite important,” Joseph added.

20. **Gender and Race Differences in the HeartMate3 LVAD as a Bridge to Transplantation**

BACKGROUND

Gender and racial disparities exist after left ventricular assist device (LVAD) implantation. Compared with older devices, the HeartMate 3 (HM3) (Abbott Cardiovascular) has demonstrated improved survival. Whether HM3 differentially improves outcomes by gender or race and ethnic groups is unknown.

OBJECTIVES

The purpose of this study is to examine differences by gender and race in the use of HM3 among patients listed for heart transplantation (HT) and associated waitlist and post-transplant outcomes.

METHODS

The authors examined all patients (20% women, 33% Black) who received LVADs as bridge to transplantation (BTT) between January 2018 and June 2020, in the OPTN (Organ Procurement and Transplantation Network) database. Trends in use of HM3 were evaluated by gender and race. Competing events of death/delisting and transplantation were evaluated using subdistribution hazard models. Post-transplant outcomes were evaluated using multivariate logistic regression adjusted for demographic, clinical, and donor characteristics.

RESULTS

Of 11,524 patients listed for HT during the study period, 955 (8.3%) had HM3 implanted as BTT. Use of HM3 increased for all patients, with no difference in use by gender (P = 0.4) or by race (P = 0.2). Competing risk analysis did not demonstrate differences in transplantation or death/delisting in men compared with women (HT: adjusted HR [aHR]: 0.92 [95% CI: 0.70-1.21]; death/delisting: aHR: 0.91 [95% CI: 0.59-1.42]), although Black patients were transplanted fewer times than White patients (HT: aHR: 0.72 [95% CI: 0.57-0.91], death/delisting: aHR: 1.36 [95% CI: 0.98-1.89]). One-year post-transplant survival was comparable by gender (aHR: 0.52 [95% CI: 0.21-1.70]) and race (aHR: 0.76 [95% CI: 0.34-1.70]), with no differences in rates of stroke, acute rejection, or graft failure.

CONCLUSIONS

Use of HM3 among patients listed for HT has increased over time and by gender and race. Black patients with HM3 were less likely to be transplanted compared with White patients, but there were no differences in post-transplant outcomes between these groups or between men and women.

21. **Pheochromocytoma: Secondary Hypertension in Pregnancy**

Introduction

A 29-year-old female patient, G5P1213, presented to an outside institution at 10 weeks' gestation with substernal chest pain, abdominal pain, blood pressure of 180/94 mm Hg, and a heart rate of 94 beats/min. Her high-sensitivity troponin level was elevated at 4,369 pg/mL (**Table 1**), but cardiac catheterization did not show coronary disease consistent with myocardial infarction nonobstructive coronary disease (MINOCA). The symptoms were attributed to a hypertensive emergency. She was subsequently referred to our cardio-obstetrics group for definitive management in the second trimester.

Table 1Laboratory Findings

	Normal	**Result**
Plasma metanephrine	0-0.49 nmol/L	7.66 nmol/L
Plasma normetanephrine	0-0.89 nmol/L	1.52 nmol/L
Urine metanephrine (24-h)	36-229 μg/d	8,929 μg/d
Urine normetanephrine (24-h)	95-650 μg/d	1,290 μg/d
Renin activity	0.2-1.6 ng/mL/h	6.0 ng/mL/h
Urine aldosterone (24-h)	1.2-28.1 μg/d	72.9 μg/d
Urine cortisol (24-h)	<59 μg/d	58.5 μg/d
Aldosterone	<16.0 ng/dL	8.4 ng/dL
B-type natriuretic peptide	<100 pg/mL	11 pg/mL
High-sensitivity troponin	<15 ng/mL	4,369 ng/mL
Thyroid stimulating hormone	0.35-4.00 mIU/mL	1.52 mIU/mL

Table 1Laboratory Findings

	Normal	Result
Urine toxicity screen	—	Negative

Learning Objectives

- To recognize clues to the presence of secondary hypertension in pregnancy.
- To differentiate pheochromocytoma from preeclampsia and other hypertensive disorders of pregnancy.
- To develop a team approach to timely diagnosis of pheochromocytoma in pregnancy.

Her past medical history included preeclampsia complicated by hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) in 2 earlier completed pregnancies and cesarean delivery. She had a history of nephrolithiasis and pyelonephritis. Outside of pregnancy, she denied a history of pre-existing hypertension, smoking, or diabetes. However, she noted a family history of coronary artery disease.

Question 1: How Do You Define Hypertension in Pregnancy?

Hypertension that develops before 20 weeks' gestation or that persists for 12 or more weeks post partum is considered chronic. Although the American College of Cardiology/American Heart Association hypertension clinical practice guidelines lowered the threshold for the diagnosis of stage 1 hypertension to 130/80 mm Hg, most global guidelines define hypertension in pregnancy as blood pressure ≥140/90 mm Hg. However, the diagnosis can be missed because of the physiological decreases in systolic and diastolic blood pressure that occur in early gestation. These decreases typically reach a nadir between 16 and 20 weeks' gestation and gradually rise to prepregnancy levels by term. Systolic blood pressure ≥160/90 mm Hg is

considered severe. Gestational hypertension refers to new onset hypertension that develops after 20 weeks' gestation without proteinuria. In contrast, preeclampsia typically occurs after 20 weeks and is often associated with proteinuria and/or end-organ dysfunction.[1] Pregnancy-associated hypertensive disorders are major contributors to maternal and fetal morbidity and mortality.[2] Although indications for initiation of therapy and goal blood pressures are evolving, appropriate therapy may reduce maternal complications without increasing fetal risk.

Question 2: What Is the Differential Diagnosis of Hypertension in Pregnancy?

The differential diagnosis of hypertension in pregnancy includes essential hypertension and secondary hypertension related to other disorders such as obstructive sleep apnea, thyroid disease, chronic kidney disease, primary aldosteronism, renal artery stenosis, Cushing syndrome, and pheochromocytoma, or it can be caused by the pregnancy itself. Initially, her early gestational age suggested chronic hypertension.

Secondary hypertension should be suspected in the setting of severe or resistant hypertension, sudden rises in previously stable patients, patients under age 30 years who are not obese in the absence of a family history, hypertension in the setting of electrolyte disorder, or age of onset before puberty.[3] A differential diagnosis scheme for secondary hypertension is shown in **Table 2**. Optimal management strategies vary by cause.[4-8] In nonpregnant patients, resistant hypertension should be considered when blood pressure remains elevated at maximum or maximally tolerated doses of 3 agents, typically including a long acting calcium-channel blocker, a renin-angiotensin system (RAAS) blocker, and a diuretic agent.[3] The diagnosis is more complicated in pregnancy because RAAS blockers are contraindicated and diuretic agents are not frequently used.

Table 2Secondary Hypertension in Pregnancy

Cause	Comments
Chronic kidney disease	Most common cause (0.9% pregnancies) May not be recognized before to pregnancy Diagnosed by elevated BUN/creatinine or reduced GFR
Obstructive sleep apnea	Consider in setting of obesity May predate pregnancy or begin during pregnancy Increasing prevalence over the pregnancy continuum May require special screening symptom tools or sleep study for diagnosis
Thyroid disease	Common cause of secondary hypertension in women aged 19-39 years, overlapping with the reproductive period Both hyperthyroidism and hypothyroidism can affect BP
Renovascular hypertension	In reproductive age group, frequently caused by fibromuscular dysplasia Consider in setting of abdominal or carotid bruit Consider with history of spontaneous coronary artery or peripheral (carotid, vertebral, renal) dissection
Primary aldosteronism	Most common form of the rarer treatable causes of secondary hypertension Consider in the setting of otherwise unexplained hypokalemia Suspect with adrenal mass Diagnosis challenging in pregnancy because of increased PRA in pregnancy; consider with PRA between 1 and 4 ng/nL/h Formal diagnosis often delayed until post partum
Pheochromocytoma	Classic triad of headache, sweating, and tachycardia Sustained or paroxysmal hypertension may present with

Table 2Secondary Hypertension in Pregnancy

Cause	Comments
	MINOCA or Takutsubo Syndrome Consider with adrenal mass
Cushing syndrome	More likely derived from an adrenal source in pregnancy Suspect with classic physical finding such as proximal muscle weakness, supraclavicular or dorsocervical fat pads, facial plethora, purple striae, truncal obesity, diabetes or glucose intolerance, abnormal menstrual cycles before pregnancy, or adrenal incidentaloma Diagnosis confirmed with 24-h urine free cortisol or midnight salivary cortisol testing
Coarctation	May manifest with hypertension in pregnancy if coarctation severity is mild or if repair occurred late Suspect with radial femoral pulse delay, when upper extremity BP is greater than or equal to lower extremity BP, or in the setting of bicuspid aortic valve Diagnosis usually confirmed by echocardiography, magnetic resonance imaging, or CT scan

BP = blood pressure; BUN = blood urea nitrogen; CT = computed tomography; GFR = glomerular filtration rate; PRA = plasma renin activity.

Laboratory testing was remarkable for an initial potassium level of 2.5 mEq/L, blood urea nitrogen of 10 mg/dL, creatinine of 0.63 mg/dL, glomerular filtration rate of 112 mL/min, and normal liver function. The initial work-up included the following: transthoracic echocardiography, revealing mild to moderate LV dysfunction with an ejection fraction of 40% to 45% and anterior and anteroseptal hypokinesis (**Video 1**); computed tomography for pulmonary embolism, which was negative; and electrocardiogram showing ST-segment and T-wave changes that were attributed to hypokalemia (**Figure 1**). She

underwent cardiac catheterization, revealing normal coronary vasculature without evidence of dissection. Of note, a renal ultrasound scan at 6 weeks' gestation showed a round left suprarenal mass measuring 3.6 cm. Additional laboratory results, which demonstrated elevated urinary catecholamines, are shown in **Table 1**.

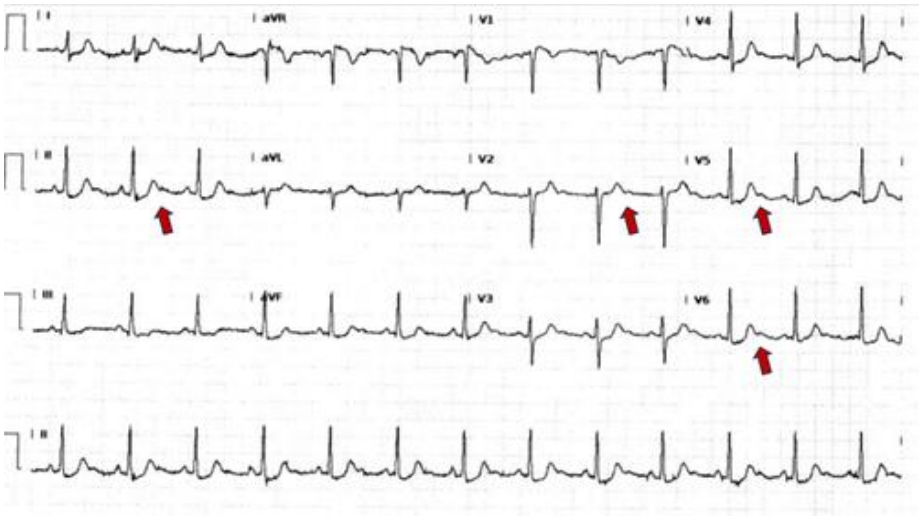

Figure 1

12-Lead Electrocardiogram at Initial Presentation

Electrocardiogram shows sinus rhythm with ST-segment depression and prominent U waves (arrows) in the precordial leads compatible with hypokalemia.

Question 3: How Do These Investigations Refine the Differential Diagnosis?

Chronic kidney disease is the most common cause of resistant hypertension in pregnancy.[4] Normal kidney function in our patient eliminated this diagnosis. This patient did not have pre-existing hypertension, thus making treatment resistance or apparent resistance unlikely. Her thyroid function was normal. Negative toxicology screen results excluded a drug-induced hypertensive emergency. The mass noted on the initial ultrasound scan and subsequent abnormal urinary catecholamines were clues prompting further investigation. When pheochromocytoma is suspected, measurements of

plasma or urinary free fractionated metanephrines have the highest diagnostic accuracy.[8]

At 22 weeks' gestation, she was evaluated by a multidisciplinary team consisting of cardiology, maternal fetal medicine, endocrinology, urology, genetic counseling, and obstetric anesthesia. Repeat transthoracic echocardiography showed normalization of left ventricular (LV) function. Abdominal magnetic resonance imaging (MRI) showed a 4.3-cm left adrenal mass concerning for pheochromocytoma (**Figures 2A** and **2B**). Magnetic resonance imaging is preferred to ultrasound for diagnosis.[8]

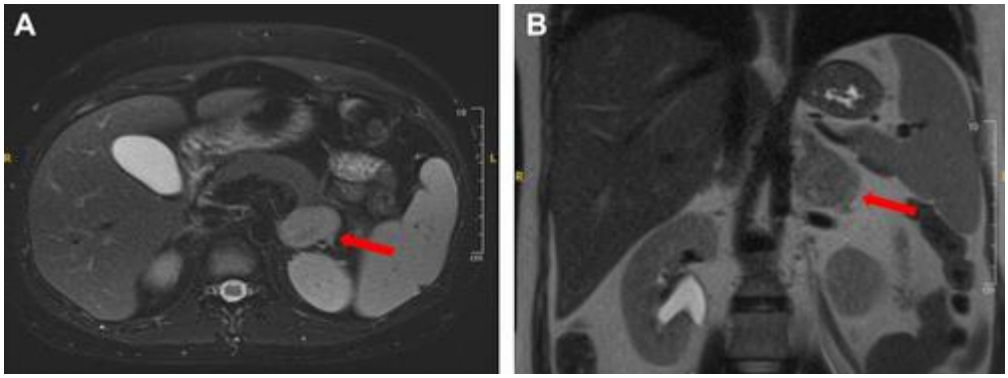

Figure 2

Pheochromocytoma: Magnetic Resonance Imaging

(A) Axial T2-weighted image of an ovoid, mildly T2-hyperintense mass in the region of the left adrenal gland (arrow). (B) Coronal image of a left adrenal mass abutting adjacent kidney (arrow).

Question 4: How Do You Manage Pheochromocytoma in Pregnancy?

Before definitive surgical management, alpha-blockade is critical to avoid perioperative hypertension and hypotension, but unlike in the nonpregnant state, orthostasis and heart rate control are more difficult to obtain because of the systemic adaptations of pregnancy. She was started on doxazosin for alpha-blockade followed by metoprolol for heart rate control.

She underwent robotic-assisted left adrenalectomy without perioperative complication. The pathologic features were consistent with pheochromocytoma (**Figures 3A to 3C**). Surgical intervention is ideally performed before 24 weeks' gestation or at/after delivery.[8] Our case is one of few reported in the literature that used robotic-assisted adrenalectomy in pregnancy. Fetal monitoring should be considered if the fetus is viable.

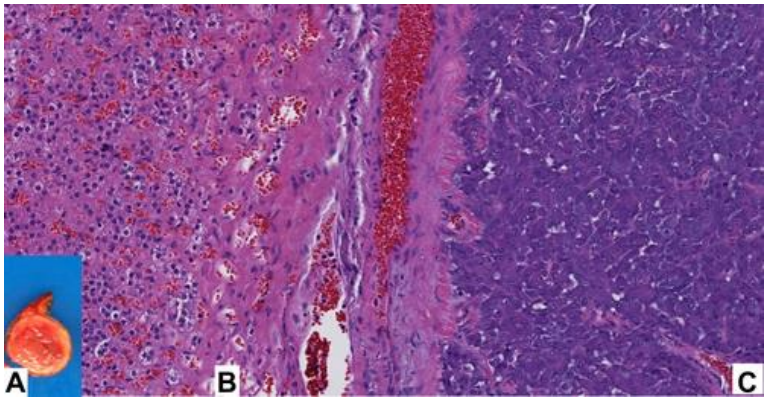

Figure 3

Pheochromocytoma: Pathologic Specimen

(A) The inset shows a gross specimen, with the lighter pink tissue rim of normal adrenal cortex and the darker tissue of the neuroendocrine-secreting tumor. (B) Normal adrenal tissue is present on the left portion of the microscopic section. (C) In contrast, the right portion shows typical polygonal and spindle-shaped cells arranged in nests (nests of Zellbalen) with prominent nucleoli and basophilic granular cytoplasm (original magnification 3B and 3C: 20x).

After resection, doxazosin was discontinued, and she was tapered off metoprolol. Blood pressure remained normal. She had an uncomplicated antepartum course. The patient underwent scheduled repeat cesarean delivery and bilateral tubal ligation. She is currently not taking any antihypertensive medications and is doing well.

Question 5: What if Surgical Management Is Deferred Until Post Partum?

If surgical treatment is deferred until post partum, adequate adrenergic blockade should occur. Without blockade, excess circulating maternal catecholamines can lead to an increased risk of adverse cardiac outcomes such as hypertensive crisis mimicking preeclampsia, myocardial infarction, cerebrovascular vascular accidents, heart failure, and maternal death. Our patient had complications of hypertensive urgency, myocardial injury, and LV dysfunction before diagnosis that made her a suitable candidate for surgical resection. Although the optimal mode of delivery is uncertain because there are limited data on vaginal delivery in women who have not undergone surgical resection, our experience suggests that cesarean delivery should be reserved for the usual obstetric indications. Treatment goals should aim to maintain uteroplacental blood flow while avoiding severe hypertension.[8] Genetic screening should be offered because one-third of cases are familial and result from an identifiable pathogenic variant.[9] Of note, the results of our patient's genetic testing for hereditary paraganglioma and pheochromocytoma were negative.

Although maternal catecholamines do not cross the placental barrier easily, uncontrolled hypertension can lead to fetal adverse outcomes, including spontaneous abortion, fetal growth restriction, preterm birth, fetal distress, and fetal demise.[1,2]

Question 6: How Can You Differentiate Pheochromocytoma From Preeclampsia?

Pheochromocytoma is estimated to occur in only 0.2 per 10,000 pregnancies, but it should be suspected in the presence of new onset hypertension at <20 weeks' gestation, paroxysmal hypertension, paroxysmal headache, orthostatic hypotension, features of heredity syndromes, or suggestive symptoms such as sweating, palpitations, headache, weakness, or anxiety.[8] Pheochromocytoma is the most common cause of adrenal tumor in pregnancy.[8]

Differentiation of pheochromocytoma from preeclampsia may be challenging, but typically preeclampsia manifests later, is associated with proteinuria and edema, and may be associated with abnormal liver enzymes and a low platelet count (HELLP syndrome), whereas pheochromocytoma manifests earlier and with paroxysmal symptoms usually in the absence of end-organ dysfunction, as noted earlier.

Perspectives

Untreated pheochromocytoma is associated with adverse maternal fetal outcomes. Work-up for secondary hypertension should be considered in the setting of pregnancy when pre-existing or new onset resistant hypertension is present, or when the patient is unresponsive to the standard antihypertensive agents commonly used in pregnancy. Early screening and intervention are essential to prevent unwarranted preterm delivery for a false diagnosis of preeclampsia. Outcomes are improved when a multidisciplinary care team is involved.

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22. Sex-specific lifetime risk of cardiovascular events: the European Prospective Investigation into Cancer-Norfolk prospective population cohort study

Aims

Better understanding of sex differences in cardiovascular disease (CVD) is essential in tailoring appropriate preventative strategies. Using a large population-based study with follow-up >25 years, we aimed to determine sex-

specific lifetime risks of incident CVD and cardiovascular (CV) mortality amongst populations with and without prevalent CVD.

Methods and results

Participants were drawn from the European Prospective Investigation into Cancer-Norfolk and followed up for a median of 26.2 years. Sex-specific lifetime risks were ascertained accounting for the competing risk of death. Models were adjusted for ethnicity and time-updated covariates: material deprivation, CV risk factors, lifestyle factors, comorbidities, and medication. A total of 23 859 participants [54.5% women; mean age (standard deviation) 59.2 (9.3) years at baseline] were included. Adjusted lifetime risks of incident CVD were higher in men than in women (69.1 vs. 57.7% at age 75): cause-specific hazard ratio (cHR) (99% confidence interval)—1.49 (1.41–1.57), while the risks of CV mortality at age 75 were 4.4% (men) and 3.1% (women): cHR—1.42 (1.31–1.54). Myocardial infarction was the predominant first presentation in men until the eighth decade. In women, the first CVD manifestations after their sixth decade were predominantly atrial fibrillation and stroke. The male-associated excess relative risks of incident CVD and CV mortality were halved in people with prevalent CVD.

Conclusion

We characterized the sex-specific lifetime CV risks in a large cohort. Men had substantially higher risk of incident CVD and CV mortality than women, which was attenuated amongst people with prevalent CVD. Our findings provide an evidence base for sex-specific CV prevention.

23. **Gender disparities in cardiovascular lifetime risk: do not forget myocardial infarction in men**

Cardiovascular disease (CVD) continues to be a major global public health challenge despite significant advancements in our understanding and management of this diverse group of conditions. Cardiovascular disease encompasses a wide spectrum of disorders, encompassing conditions caused by atherosclerosis such as acute and chronic coronary syndrome and peripheral vascular disease and conditions with a more heterogenous

causality such as stroke, heart failure, and atrial fibrillation. While CVD overall affects both men and women, the prevalence, aetiology, and outcomes often differ substantially between the sexes. In recent years, the epidemiology of CVD has undergone notable changes. Although more women than men are now losing their lives to CVD, the condition still predominantly affects men when it comes to premature mortality.1 This shift is dynamic and influenced by several gender-specific risk factors as well as distinct risk profiles. Men tend to exhibit a higher prevalence of lifestyle-related risk. This includes a higher rate of smoking, a less heart-healthy diet, and excessive alcohol consumption. These behaviours have long been recognized as contributors to CVD. In contrast, women experience hormonal changes throughout their lives, including menarche, pregnancy, and menopause. Additionally, women tend to be less physically active than men, which may impact CVD risk. Furthermore, evidence suggests that psychological stress and socioeconomic disparities affect women more profoundly, potentially contributing to an increased susceptibility to CVD.

Pana et al.'s study in this issue of European Journal of Preventive Cardiology contributes important insights into the sex-specific lifetime risks of cardiovascular events.2 Drawing upon data from the European Prospective Investigation into Cancer (EPIC) cohort in Norfolk, which monitored 23 859 participants aged 40 or more for a median of 26.2 years, they describe the sex-specific lifetime risks for myocardial infarction (MI), cerebrovascular accident, atrial fibrillation, this research paints a detailed picture of the lifetime risks associated with various cardiovascular conditions.

Overall, the study confirmed the higher lifetime risk in men of all incident CVD as well as CVD mortality. Their lifetime risk is approximately 40–50% higher than that of women. While the male disadvantage was present for all the conditions studied, the largest differences were seen for the atherosclerotic CVD (ASCVD), notably MI and peripheral artery disease. In contrast, gender differences in stroke and valvular heart disease were less pronounced. Although men had a higher lifetime risk of atrial fibrillation, this condition rises steeply around age 70 in women and was the dominating first

cardiovascular event due to the much lower risk of MI in women at younger ages.

The study also included adjustment for available information on demographic characteristics, behavioural parameters, lifestyle attributes, blood pressure, biomarkers, and medication. Somewhat surprisingly adjustment for these had a minor impact on the observed differences in lifetime trajectories between men and women. This suggests that over the years, the significant gender disparities in lifestyle, which were prominent decades ago and contributed to a surge in heart attacks in middle-aged men, have substantially diminished. Under the presumption that risk factors with substantial gender differences in distribution or impact have been included, the remaining gender differences in lifetime risk of CVD remain unexplained by modifiable risk factors. Whether these then are solely attributable to biological distinctions is unknown.

The study conducted by Pana et al. exhibits several strengths. These include its substantial size enabling robust statistical analyses. The availability of detailed data on potential confounding and explanatory factors further enhances the credibility of the findings. This would not have been possible from a similar analysis based on health statistics data. Additionally, the long follow-up period gives a stronger perspective. However, the study is not without limitations. Questions about the generalizability of the findings arise, though the specific gender disparities are unlikely to be substantially affected by such concerns. The extended follow-up period, although generally a strength also means that some of the gender differences observed may reflect an earlier era. The baseline assessments occurred in 1993–98, nearly three decades ago. During this time, both the underlying risk of CVD changed in the UK population and the risk profiles of the individuals studied have likely changed, something which the study could only partly capture.

The field of gender differences in the lifetime risk of developing CVD is intricate and ever evolving. By comprehensively examining gender-specific risk factors, hormonal influences, symptom presentation, and disparities in healthcare,

we can work towards a future where CVD does not discriminate based on gender. Such efforts are essential for reducing the overall burden of CVD and promoting lifelong cardiovascular health of all individuals. The current analyses emphasize the importance of prevention, particularly for MI in men after the age of 50. Although the presence of risk factors did not affect the gender differences, a significant percentage of heart attacks remain preventable through lifestyle changes and control of risk factors. WHO estimates that more than 80% of CVD is preventable.3 There is still considerable room for improvement in CVD prevention. Smoking, although decreasing in many countries, remains a concern, especially among men in middle-income countries.4 Physical inactivity affects an estimated one in three adults living in ESC member countries: dietary factors, an underestimated risk factor for ASCVD is increasingly dominated by larger amounts of sugar-sweetened beverages and processed food with high content of salt and saturated fat. Prevalence of obesity is still increasing across all ESC countries and elevated blood pressure is not well-controlled on a population level. The same is true for the prevalence of elevated blood cholesterol.5 Added to this are the exposures that are less amenable for intervention for the individual—environmental risk factors related to pollution and climate change as well as psychosocial stress related to job and modern life.6 Many of these risk factors are a higher burden in middle-income countries causing the higher rates of ASCVD seen in these countries than in Western populations such as that included in the EPIC study.

In conclusion, the study by Pana et al. serves as a remained of the continued need for a strong focus on prevention. Even if only a minor part of gender differences can be attributed to disparities in exposure, the higher rates of MI in younger men remain a cause for concern and should be a priority for preventive action.

24. Standardized longitudinal strain curves stratified by age and sex in healthy individuals: The Copenhagen City Heart Study

Introduction

Speckle-tracking echocardiography has gained widespread use, and strain parameters such as global longitudinal strain (GLS) and strain rates are strongly associated with risk of heart failure and cardiovascular death. Such strain measures, however, only represent limited features of the complete longitudinal strain (LS) curve. Thus, interpretation of entire curves might provide additional insight.

Purpose

To establish normal standardized LS curves over an entire heart cycle for healthy subjects stratified by age and sex. Furthermore, to assess how these curves vary with age and to compare this with conventional strain measures.

Methods

The study population consisted of 1790 healthy subjects free of cardiovascular disease and risk factors including diabetes mellitus and hypertension at baseline. Subjects were stratified by sex and further by age in groups as defined in the SCORE risk chart. Subjects underwent echocardiography, and LS curves from the apical four-chamber view were derived and standardized in length using linear interpolation. Terms to describe qualitative findings in the standardized strain curves were established (Figure 1). Early diastolic strain (EDS) was defined as the difference in strain from peak LS to maximal curvature after early diastolic filling, while late diastolic strain (LDS) was defined as the difference in strain from the plateau phase in late passive diastole to maximal curvature in active diastole. Conventional strain measures included GLS, systolic strain rate (SRS), early diastolic strain rate (SRE), and late diastolic strain rates (SRA). The association between these and age group were investigated using univariable linear regression for each sex.

Results

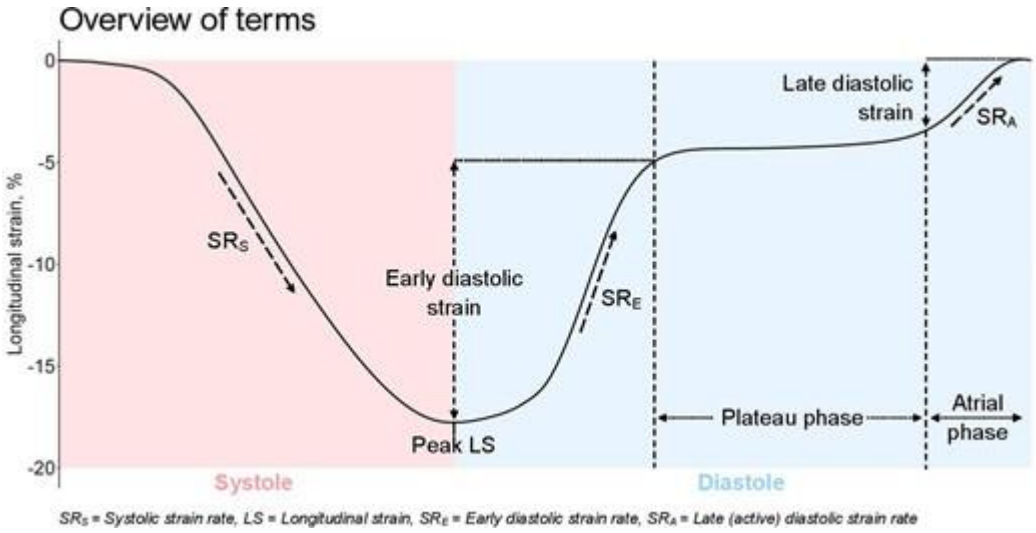
In the study population, 1101 (61.5%) subjects were female. The standardized strain curves (Figure 2) showed that aging primarily manifested in the diastolic part of the strain curve. Decreasing EDS was associated with increasing age group, while the opposite was true for LDS. In linear regression, both SRE (female: beta=-0.13; $p<0.001$, male: beta=-0.1; $p<0.001$)

and SRA (female: beta=0.09; p<0.001, male: beta=0.09; p<0.001) were associated with age group for both sexes. Peak LS did not change notably with age, and in linear regression, GLS and SRS were only significantly associated with age for women (GLS: beta=0.12; p<0.001, SRS: beta=0.01; p<0.001).

Conclusion

We derived normal standardized LS curves for healthy individuals stratified by age and sex, which can serve as normal values in future studies. In addition, these showed that age was primarily associated with changes in the diastolic part of the strain curve in both sexes, which was consistent with conventional strain measures.

Figure 1:



18. Clinical Outcomes by Sex After Pulsed Field Ablation of AF

Study Questions:

What are the sex differences in patients undergoing pulsed field ablation (PFA) for atrial fibrillation (AF) in the MANIFEST-PF (Multinational Survey on the Methods, Efficacy, and Safety on the Postapproval Clinical Use of Pulsed Field Ablation) registry?

Methods:

The authors analyzed clinical data from the MANIFEST-PF registry of all consecutive patients who underwent first-ever PFA for paroxysmal or persistent AF.

Results:

The study included a total of 1,568 patients (male, 65%). Female patients, as compared with male patients, were older (age 68 vs. 62 years), had more paroxysmal AF (70% vs .62%), and had fewer comorbidities. Pulmonary vein isolation was performed in 99.8% of female and 98.9% of male patients. Additional ablation was performed in 22% of female and 23% of male patients. The 1-year freedom from atrial arrhythmia was similar in male and female patients (79% vs. 76%). There was no significant difference in acute major adverse events between groups (male 1.5% vs. female 2.5%).

Conclusions:

The study included a total of 1,568 patients (male, 65%). Female patients, as compared with male patients, were older (age 68 vs. 62 years), had more paroxysmal AF (70% vs .62%), and had fewer comorbidities. Pulmonary vein isolation was performed in 99.8% of female and 98.9% of male patients. Additional ablation was performed in 22% of female and 23% of male patients. The 1-year freedom from atrial arrhythmia was similar in male and female patients (79% vs. 76%). There was no significant difference in acute major adverse events between groups (male 1.5% vs. female 2.5%).

Perspective:

MANIFEST-PF demonstrated similar clinical effectiveness with PFA in both male and female individuals for both paroxysmal and persistent AF. This is the first study examining PFA for AF, which reported clinical outcomes according to sex. Prior studies of traditional radiofrequency ablation and cryoablation showed variable outcomes across gender, and some of them reported a higher risk of procedure-associated complications such as cardiac tamponade, stroke/transient ischemic attack, vascular complications, and

major bleeding in female patients compared with male patients. The absence of sex differences for major adverse events in the present study suggests improved safety of AF ablation in part due to advanced “single-shot” PFA technology that minimizes catheter manipulation in the left atrium.

19. Sex differences in symptoms of anxiety, depression, post-traumatic stress disorder, and cognitive function among survivors of out-of-hospital cardiac arrest

Aims

Anxiety, depression, and post-traumatic stress disorder (PTSD) among out-of-hospital cardiac arrest (OHCA) survivors may impact long-term recovery. Coping and perception of symptoms may vary between sexes. The aim was to explore sex differences in psychological consequences following OHCA.

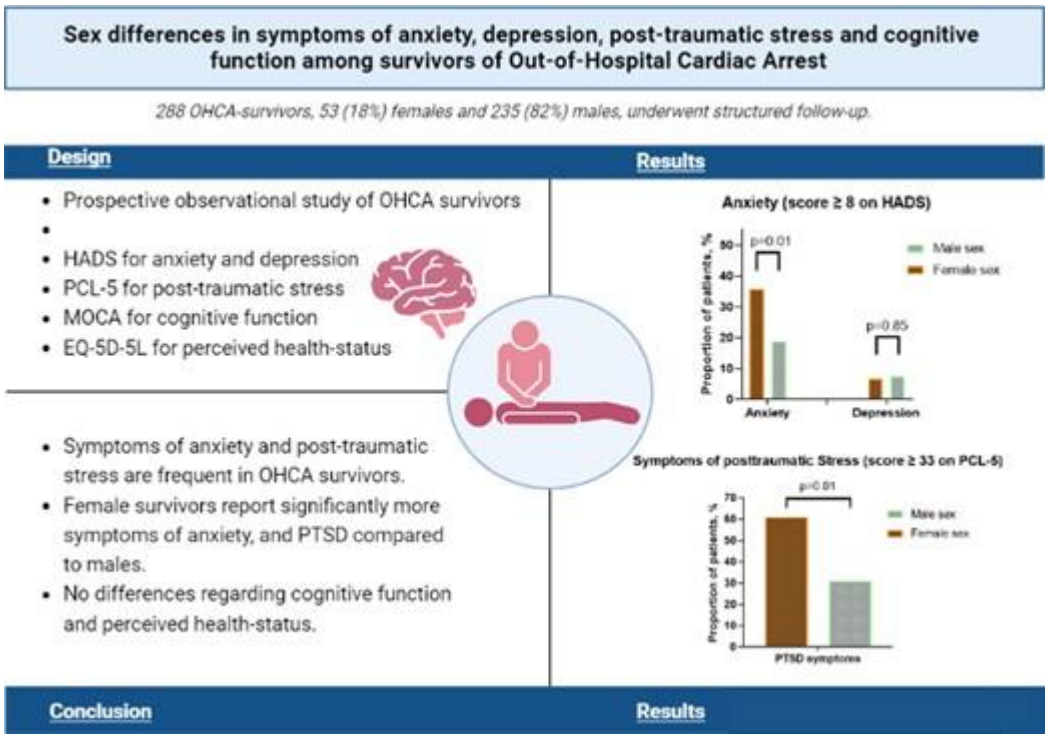
Methods and results

This was a prospective observational study of OHCA survivors who attended a structured 3-month follow-up. Symptoms of anxiety/depression were measured using the Hospital Anxiety and Depression Scale, range 0–21, with a cut-off score of ≥8 for significant symptoms; PTSD was measured with the PTSD Checklist for DSM-5 (PCL-5), range 0–80. A score of ≥33 indicated PTSD symptoms. Cognitive function was assessed by the Montreal Cognitive Assessment. From 2016 to 2021, 381 consecutive comatose OHCA survivors were invited. Of these, 288 patients (76%) participated in the follow-up visit [53 (18%) females out of 80 survivors and 235 (82%) males out of 300 alive at follow-up (78%)]. Significant symptoms of anxiety were present in 47 (20%) males and 19 (36%) females (P = 0.01). Significant symptoms of PTSD were present in 30% of males and 55% of females (P = 0.01). Adjusting for pre-specified covariates using multivariable logistic regression, female sex was significantly associated with anxiety [odds ratio (OR): 2.18, confidence interval (CI): 1.09–4.38, P = 0.03]. This difference was especially pronounced among young females (below median age, $OR_{adjusted}$: 3.31, CI: 1.32–8.29, P = 0.01) compared with young males. No significant sex difference was observed for depression or cognitive function.

Conclusion

Symptoms of anxiety and PTSD are frequent in OHCA survivors, and female survivors report significantly more symptoms of anxiety and PTSD compared with males. In particular, young females were significantly more symptomatic than young males.

Graphical Abstract



20. **Higher cardiovascular risk for women throughout the glycaemic spectrum: only a question of sex?**

- This is an observational, cohort study, based on data from the UK Biobank and funded by Diabetes UK and British Heart Foundation, aimed at assessing sex-specific risk for cardiovascular disease (CVD) across the whole glycaemic spectrum and characterizing the contribution of clinical and lifestyle factors to sex-related differences.1
- From 2006 to 2010, a total number of 502 398 subjects aged 40–69 were recruited across England, Scotland, and Wales and followed through 2021. Every participant underwent baseline assessment for sociodemographic, clinical, and lifestyle characteristics and blood

sampling for biomarker measurement. Based on glycated haemoglobin (HbA1c) levels, participants were categorized as (i) low-normal (<35 mmol/mol or <5.5%, including 47% of the entire population), (ii) normal (35–41 mmol/mol or 5.5%–5.9%, including 44% of the entire population), (iii) pre-diabetes (42–47 mmol/mol or 6.0%–6.4%, including 3% of the entire population), (iv) undiagnosed diabetes (≥48 mmol/mol or ≥6.5%, including 1% of the entire population), and (v) diagnosed diabetes (based on medical history and use of glucose-lowering medications, including 4% of the entire population).

- Outcomes included coronary artery disease (CAD), atrial fibrillation, deep vein thrombosis, pulmonary embolism, stroke, and heart failure, as well as a composite outcome of any CVD on its first occurrence. For the analysis of any CVD, individuals who had any CVD prior to baseline were excluded. Similarly, for the analysis of each outcome, individuals who had the respective event prior to baseline were excluded.
- Covariates were selected based on known determinants of HbA1c levels and CVD and included sociodemographic factors (i.e. age, sex, ethnicity, and index of multiple deprivation), mostly self-reported lifestyle [i.e. smoking status, alcohol consumption, physical activity, body mass index (BMI), waist–hip ratio, and dietary intake], and clinical characteristics (i.e. total cholesterol, serum creatinine, C-reactive protein, diagnosed hypertension, use of antihypertensive drugs or statins, and family history of CVD).
- The final analysis included 427 435 participants, of whom 195 752 (45.8%) men and 231 683 (54.2%) women. Both men and women in higher HbA1c categories had higher BMI, poorer renal function, greater prevalence of hypertension, and use of antihypertensive medications or statins compared with their counterparts with low-normal or normal HbA1c levels. Over a median 12-year follow-up, age-standardized incidence rates for any CVD were 16.9 and 9.1 events/1000 person-years for men and women, respectively. Both men and women with pre-diabetes, undiagnosed diabetes, and, more markedly, diagnosed diabetes had higher CVD rates than those with normal HbA1c. In

contrast, CVD rates were lower in those with low-normal HbA1c compared with normal HbA1c. The relative associations between diagnosed diabetes and any CVD were more pronounced in women than in men: age-adjusted hazard ratios (HRs) were 1.55 [95% confidence interval (CI), 1.49–1.61] in men and 2.00 (95% CI, 1.89–2.12) in women (P for interaction <.0001). Compared with those with normal HbA1c, the risk of CVD was also higher in pre-diabetes and undiagnosed diabetes groups, with age-adjusted HRs ranging from 1.30 to 1.47, with relative increases higher for women. In addition, both women and men with low-normal HbA1c were at decreased risk of CVD (HR 0.86, 95% CI, 0.84–0.98 and 0.86, 0.84–0.88, respectively).

- These associations attenuated after additional adjustment for clinical and lifestyle factors, particularly BMI, waist–hip ratio, and antihypertensive or statin use. However, the increased risk of CVD remained higher in both sexes with diagnosed diabetes (fully adjusted HR: 1.06, 95% CI, 1.02–1.11 for men and 1.17, 1.10–1.24 for women; P for interaction = .0387).

21. Cardiac Remodeling After Hypertensive Pregnancy Following Physician-Optimized Blood Pressure Self-Management

Hypertensive pregnancy disorders are associated with adverse cardiac remodeling, which can fail to reverse postpartum in some women. The Physician Optimized Postpartum Hypertension Treatment trial demonstrated improved blood pressure control, while the cardiovascular system recovers postpartum, associates with persistently reduced blood pressure. We now report the impact on cardiac remodeling.

METHODS

In this prospective, randomized, open-label, blinded endpoint trial, in a single UK hospital, 220 women were randomly assigned 1:1 to self-monitoring with research physician-optimized antihypertensive titration, or usual postnatal

care from primary care physician and midwife. Participants were aged 18 years or over, with pre-eclampsia or gestational hypertension, requiring antihypertensives on hospital discharge postnatally. Pre-specified secondary cardiac imaging outcomes were recorded by echocardiography around delivery, and again at blood pressure primary outcome assessment, around nine months postpartum, when cardiovascular magnetic resonance was also performed.

RESULTS

187 women (101 intervention; 86 usual care) underwent echocardiography at baseline and follow up, at a mean 258+/-14.6 days postpartum, of which 174 (93 intervention; 81 usual care) also had cardiovascular magnetic resonance at follow up. Relative wall thickness by echocardiography was 0.06 (95% CI0.07 to 0.05, P=<0.001) lower in the intervention group between baseline and follow up, and cardiovascular magnetic resonance at follow up demonstrated a lower left ventricular mass (-6.37g/m2 (95% CI -7.99 to -4.74, P<0.001), end diastolic volume (-3.87ml/m2, 95% CI -6.77 to -0.98, P=0.009) and end systolic volume (-3.25ml/m2, 95% CI 4.87 to -1.63, P <0.001) and higher left and right ventricular ejection fraction by 2.6% (95% CI 1.3 to 3.9, P<0.001) and 2.8% (95% CI 1.4 to 4.1, P<0.001) respectively. Echocardiography assessed left ventricular diastolic function demonstrated a mean difference in average E/E' of 0.52 (95% CI -0.97 to -0.07, P=0.024), and a reduction in left atrial volumes of -4.33ml/m2 (95% CI -5.52 to -3.21, P=<0.001) between baseline and follow up, when adjusted for baseline differences in measures.

CONCLUSIONS

Short-term postnatal optimization of blood pressure control following hypertensive pregnancy, through self-monitoring and physician-guided antihypertensive titration, associates with long term changes in cardiovascular structure and function, in a pattern associated with more favorable cardiovascular outcomes.

22. AHA: Self-Monitoring, Remote Physician-Guided Titration Aids Postpartum BP Control

The combination of self-monitoring and physician-guided titration of antihypertensive medications is associated with lower postpartum blood pressure following a hypertensive pregnancy compared with usual postnatal outpatient care, according to a study published online Nov. 11 in the Journal of the American Medical Association to coincide with the American Heart Association Scientific Sessions 2023, held from Nov. 11 to 13 in Philadelphia.

Jamie Kitt, D.Phil., from the University of Oxford in the United Kingdom, and colleagues assessed whether remote self-monitoring and physician-guided titration of antihypertensive medications using a Bluetooth-enabled app provides better long-term blood pressure control than usual outpatient care during the first nine months postpartum. The analysis included 200 participants randomly assigned following a hypertensive pregnancy.

The researchers found that the 24-hour mean diastolic blood pressure, measured at 249 days postpartum, was 5.8 mm Hg lower in the intervention group (71.2 versus 76.6 mm Hg) than in the control group (between-group difference, −5.80 mm Hg). Similar results were seen for 24-hour mean systolic blood pressure (114.0 versus 120.3 mm Hg; between-group difference, −6.51 mm Hg).

"An intervention that lowers blood pressure by 5 mm Hg would be expected to delay progression to hypertension by many years and, over a lifetime, reduce risk of cardiovascular or cerebrovascular events," the authors write.

23. Maternal Depressive Symptoms May Start at Pregnancy

Maternal depressive symptoms probably start at or before pregnancy, with trajectories that remain stable across the perinatal into the postnatal period, new research suggests.

The analysis of more than 11,000 pregnant women with depressive symptoms from seven prospective cohorts in Canada, the United Kingdom, and

Singapore suggests that depressive symptoms (low, mild, or high levels) start sooner and last longer than is commonly thought.

The term "postnatal depression" is "at odds with existing scientific literature and the experience of clinicians who treat mental disorders in the context of obstetric practice," said Michael J. Meaney, PhD, professor at McGill University, Montreal, Quebec, and director of the Translational Neuroscience Program at the Agency for Science, Technology and Research (A*STAR), Singapore.

"Although we anticipated that the prenatal period would be the primary time of onset and that symptom levels would be largely stable, I was nevertheless surprised at how this pattern was so universal across so many studies," he said, speaking to Medscape Medical News. "In truth, we saw very little evidence for a postnatal onset."

This suggests that depressive symptoms start earlier than previously thought, and "that the relevant clinical settings for prevention are those treating women in routine health care, including family medicine," he added.

Start Screening Sooner

The investigators examined the course and stability of self-reported depressive symptoms at multiple time points across the perinatal period among 11,563 pregnant women in seven cohorts from the United Kingdom, Canada, and Singapore. Participants' mean age was 29 years; 87.6% were White, 4.9% were East Asian, and 2.6% were Southeast Asian.

The analysis tracked depressive symptoms from preconception through pregnancy to 2 years after childbirth. Three groups of mothers were identified in each cohort on the basis of their level of depressive symptoms (low, mild, or high) as assessed by the Edinburgh Postnatal Depression Scale (EPDS) or the Center for Epidemiological Studies Depression (CES-D).

The team found that all mothers within and across all cohorts had stable trajectories of maternal depressive symptoms from pregnancy onward. Trajectories for mothers who passed clinically validated cutoffs for "probable" depression also showed stable trajectories from pregnancy into the postnatal period.

"Taken together, these findings suggest that maternal depressive symptom levels in community-based cohort studies are apparent during pregnancy and remain stable into the postnatal period," the authors write. "The results point to the early antenatal period as a timepoint for the identification of stable trajectories of maternal depressive symptoms. Public health policies should emphasize the early antenatal period as the optimal timing for interventions targeting maternal depressive symptoms."

The findings, they note, "underscore the American Psychiatric Association's recent approach in renaming postpartum depression as peripartum depression."

Furthermore, a recent paper of the group's findings details that depressive symptoms may often predate conception.

"Our findings should serve to universally align practice to prenatal screening," even though depression screening often takes place in a mid-gestational visit during the second trimester, Meaney said. "Our findings and those on the effects on child development strongly suggest the timing of the screening must be advanced into the first confirmation of pregnancy."

Depression Is Likely Worse in the United States

Catherine Monk, PhD, who is chief of the Division of Women's Mental Health and professor of medical psychology at Columbia University Vagelos College of Physicians and Surgeons in New York, commented on the study for Medscape Medical News.

"The results of this well-conducted and important study amplify similar research findings and the experience of most perinatal clinicians: depression is stable from pregnancy onwards," said Monk, who was not involved in the research. "As the authors note, the common focus on postpartum depression misses the months of prior suffering and an opportunity for earlier intervention."

Monk would have liked the results to have been examined further by race and ethnicity and socioeconomic factors, she noted. "Also, the combined sample does not include a US cohort. This is significant as the US has the highest maternal morbidity and mortality rate of developed nations, and some reports identify mental health factors as the number-one cause of maternal mortality."

"Given the tremendous economic, racial, and ethnic inequities in healthcare — the lack of any kind of health justice — it is quite possible that in the US, depression that starts in pregnancy worsens over time, at least for some demographic groups," she said. "Rates of depression, levels of depression, and the course of it during the peripartum period may be even more dire [in the US] than what is represented in this article."

"What should be practice-changing about this article, and so many others demonstrating the persistent, and often high levels of life-threatening depression during pregnancy, is the need for mental health providers to advocate for changes to the low rates of insurance reimbursement that push providers away from accepting insurance and into private practice, making access to affordable mental care nearly impossible for most," she concluded.

24. Better Postpartum BP Control With Self-Monitoring: POP-HT

Self-monitoring blood pressure (BP) during the early postpartum period may take advantage of a "critical window" when better BP monitoring could prevent

later cardiovascular events in women who have hypertensive pregnancies, new research suggests.

In a randomized trial of 220 women with preeclampsia or gestational hypertension, those who took daily postpartum BP readings and received clinician-guided advice for titrating antihypertensives had a 5 mm Hg lower average diastolic BP at 9 months, compared with those receiving usual care.

Jamie Kitt, DPhil, from the University of Oxford, Oxford, England, presented these findings from the Physicians Optimized Postpartum Hypertension Treatment (POP-HT) clinical trial at the American Heart Association (AHA) 2023 Scientific Sessions. The study was simultaneously published online in JAMA, and a cardiac imaging substudy was published online in Circulation.

"This trial identifies a potential need for a paradigm shift in the way women affected by hypertensive pregnancy are managed postnatally," Kitt said. "If a 5 mm Hg improvement in BP is maintained longer term, it can result in about a 20% reduction in lifetime cardiovascular risk."

The imaging substudy suggests that short-term postnatal optimization of BP control following hypertensive pregnancy through self-monitoring and physician-guided antihypertensive titration is linked with better cardiac remodeling changes seen by cardiovascular magnetic resonance and echocardiography.

POP-HT "proves for the first time that the first few weeks after delivery are a critical time that can determine the long-term cardiovascular health of the mother," senior author Paul Leeson, PhD, also from the University of Oxford, who presented the findings in a press briefing, told theheart.org | Medscape Cardiology.

"Interventions during this period can have long-term beneficial impacts on cardiovascular health," he said. "These findings rewrite the textbook on our understanding of how and why hypertensive pregnancies associate with later cardiovascular disease in the mother."

Next, Leeson said, "We need to work out the best ways to implement these interventions "at scale. Then we can ensure all women who have hypertensive pregnancies can get access to the long-term cardiovascular benefits we have

demonstrated are possible through improving postpartum cardiac care," he said, adding that "this is entirely achievable using current available technologies."

Hypertension in Pregnancy

About 1 in 10 pregnant women develop hypertension in pregnancy (preeclampsia or gestational hypertension), and 1 in 3 such women go on to develop chronic hypertension within 10 years, "when they are usually still in their 30s or 40s," Leeson said.

During pregnancy, the heart remodels to cope with pregnancy and it undergoes more severe changes if BP is high. Then during the 6 weeks after giving birth, this remodeling rapidly reverses.