News in March 2023

1. In Utero Exposure to Asthma Medication Not Tied to Risks of Neurodevelopmental Disorders

Use of asthma medication by pregnant women was not associated with an increased risk of autism, attention-deficit/hyperactivity disorder, or Tourette syndrome for their children, a new study shows.

The drugs included in the study were leukotriene-receptor antagonists (LTRAs), which are often used to treat allergic airway diseases, including asthma and allergic rhinitis.

"Over the years, the U.S. Food and Drug Administration has monitored post-marketing data about the potential harm of neuropsychiatric events (NEs) associated with montelukast, the first type of LTRAs, and issued boxed warnings about serious mental health side effects for montelukast in 2020," said corresponding author Tsung-Chieh Yao, MD, of Chang Gung Memorial Hospital, Taiwan, in an interview.

However, evidence of a link between NEs and LTRA use has been inconsistent, according to Dr. Yao and colleagues.

"To date, it remains totally unknown whether the exposure to LTRAs during pregnancy is associated with the risk of neuropsychiatric events in offspring," said Dr. Yao.

To address this question, the researchers used data from National Health Insurance Research Database in Taiwan to identify pregnant women and their offspring from 2009 to 2019. The initial study population included 576,157 mother-offspring pairs, including 1,995 LTRA-exposed and 574,162 nonexposed children.

The women had a diagnosis of asthma or allergic rhinitis; multiple births and children with congenital malformations were excluded. LTRA exposure was defined as any dispensed prescription for LTRAs during pregnancy. Approximately two-thirds of the mothers were aged 30-40 years at the time of delivery.

The findings were published in a research letter in JAMA Network Open.

In the study population at large, the incidence of the three neurodevelopmental disorders ADHD, autism spectrum disorder (ASD), and Tourette syndrome was not significantly different between those children exposed to LTRAs and those not exposed to LTRAs in utero (1.25% vs. 1.32%; 3.31% vs. 4.36%; and 0.45% vs. 0.83%, respectively).

After propensity score matching, the study population included 1,988 LTRA-exposed children and 19,863 nonexposed children. In this group, no significant

associations appeared between prenatal LTRA exposure and the risk of attention-deficit/hyperactivity disorder (adjusted hazard ratio, 1.03), autism spectrum disorder (AHR, 1.01), and Tourette syndrome (AHR, 0.63).

Neither duration nor cumulative dose of LTRA use during pregnancy showed an association with ADHD, ASD, or Tourette syndrome in offspring. Duration of LTRA use was categorized as shorter or longer periods of 1-4 weeks vs. more than 4 weeks; cumulative dose was categorized as 1-170 mg vs. 170 mg or higher.

The findings were limited by the lack of randomization, inability to detect long-term risk, and potential lack of generalizability to non-Asian populations, and more research is needed to replicate the results, the researchers noted. However, the current findings were strengthened by the large study population, and suggest that LTRA use in pregnancy does not present a significant risk for NEs in children, which should be reassuring to clinicians and patients, they concluded.

The current study is the first to use the whole of Taiwan population data and extends previous studies by examining the association between LTRA use during pregnancy and risk of neuropsychiatric events in offspring, Dr. Yao said in an interview. "The possibly surprising, but reassuring, finding is that prenatal LTRA exposure did not increase risk of ADHD, ASD, and Tourette syndrome in offspring," he said.

"Clinicians prescribing LTRAs such as montelukast (Singulair and generics) to pregnant women with asthma or allergic rhinitis may be reassured by our findings," Dr. Yao added. The results offer real-world evidence to help inform decision-making about the use of LTRAs during pregnancy, although additional research is needed to replicate the study findings in other populations, he said.

The study was supported by the National Health Research Institutes, Taiwan, the Ministry of Science and Technology of Taiwan, the National Science and Technology Council of Taiwan, and the Chang Gung Medical Foundation. The researchers had no financial conflicts to disclose.

2. Pfizer Ready to Launch RSV Vaccines for Older Adults, Pregnant Women in US, Europe

U.S. drugmaker Pfizer is ready to launch its respiratory syncytial virus (RSV) vaccine for both older adults and pregnant women in the United States and Europe later this year, executives said on Thursday.

Both Pfizer and British drugmaker GSK have RSV vaccines they hope to launch in the United States and Europe this year, pending regulators' approval.

“We are anticipating approval in both the U.S. and Europe in time for rollout in the fall,” Kena Swanson, Pfizer head of viral vaccines research & development, told a media briefing at the company's biggest manufacturing and packaging site globally.

RSV is a leading cause of pneumonia in infants and the elderly, and decades of research have finally resulted in the two successful vaccines Pfizer and GSK are racing to introduce.

Some 14,000 people die annually in the United States of the lower respiratory tract disease caused by the virus, and analysts see a multibillion-dollar market for the vaccine by the end of the decade.

A GSK executive on Wednesday told Reuters that it was also ready to launch its RSV vaccine for older adults in the United States this year without supply constraints.

Neither company would say how many doses of their vaccines they intended to have ready for their respective launches.

The U.S. Food and Drug Administration (FDA) is expected to approve both vaccines for people aged 60 and above by May, while an FDA decision on the use of Pfizer's vaccine for pregnant women is due in August. The EU's decision, which could pave the way for the vaccines to be introduced in the UK as well, are due in the second half of the year.

Annaliesa Anderson, Pfizer head of vaccines research & development, told the same briefing that the company anticipates a population of about 4 million pregnant women annually in the United States who could eventually receive its RSV vaccine, though the market will take time to shape.

She later told Reuters that the so-called "tripledemic" that hit the northern hemisphere this winter may have at least temporarily raised awareness of RSV, which despite its dangers for the very old and very young is not well known by the public.

"In the U.S. (this winter), the pediatric hospitals were full of babies all with RSV...it certainly hit the news and people were much more aware," she said.

Given how contagious the virus is, the best way to protect infants from contracting the virus and becoming severely ill is by vaccinating their mothers during pregnancy, Anderson said.

GSK last year voluntarily stopped its clinical trial of its own RSV vaccine on pregnant women and is currently only pursuing the use of its vaccine on older adults, a company spokesperson told Reuters on Thursday.

3. Maternal Outcomes in Pregnant Women With CHD-Associated Pulmonary Hypertension

BACKGROUND

Studies focused on pregnant women with congenital heart disease (CHD)-associated pulmonary hypertension (PH) are scarce and limited by small sample sizes and single-center design. This study sought to describe the pregnancy outcomes in women with CHD with and without PH.

METHODS

Outcomes for pregnant women with CHD were evaluated retrospectively from 1993 to 2016 and prospectively from 2017 to 2019 from 7 tertiary hospitals. PH was diagnosed on the basis of echocardiogram or catheterization. The incidence of maternal death, cardiac complications, and obstetric and offspring complications was compared for women with CHD and no PH, mild, and moderate-to-severe PH.

RESULTS

A total of 2220 pregnant women with CHD had completed pregnancies. PH associated with CHD was identified in 729 women, including 398 with mild PH (right ventricle to right atrium gradient 30-50 mm Hg) and 331 with moderate-to-severe PH (right ventricle to right atrium gradient >50 mm Hg). Maternal mortality occurred in 1 (0.1%), 0, and 19 (5.7%) women with CHD and no, mild, or moderate-to-severe PH, respectively. Of the 729 patients with PH, 619 (85%) had CHD-associated pulmonary arterial hypertension, and 110 (15%) had other forms of PH. Overall, patients with mild PH had better maternal outcomes than those with moderate-to-severe PH, including the incidence of maternal mortality or heart failure (7.8% versus 39.6%; $P<0.001$), other cardiac complications (9.0% versus 32.3%; $P<0.001$), and obstetric complications (5.3% versus 15.7%; $P<0.001$). Brain natriuretic peptide >100 ng/L (odds ratio, 1.9 [95% CI, 1.0-3.4], $P=0.04$) and New York Heart Association class III to IV (odds ratio, 2.9 [95% CI, 1.6-5.3], $P<0.001$) were independently associated with adverse maternal cardiac events in pregnancy with PH, whereas follow-up with a multidisciplinary team (odds ratio, 0.4 [95% CI, 0.2-0.6], $P<0.001$) and strict antenatal supervision (odds ratio, 0.5 [95% CI, 0.3-0.7], $P=0.001$) were protective.

CONCLUSIONS

Women with CHD-associated mild PH appear to have better outcomes compared with women with CHD-associated moderate-to-severe PH, and with event rates

similar for most outcomes with women with CHD and no PH. Multimodality risk assessment, including PH severity, brain natriuretic peptide level, and New York Heart Association class, may be useful in risk stratification in pregnancy with PH. Follow-up with a multidisciplinary team and strict antenatal supervision during pregnancy may also help to mitigate the risk of adverse maternal cardiac events.

4. Oral Contraceptive Pills and Hypertension

Oral contraceptive pills (OCPs) have been used as effective and popular forms of contraception since the middle of the last century. By 2019, over 150 million reproductive-aged individuals were using OCPs to prevent unintended pregnancies worldwide. Safety concerns regarding the effects of OCPs on blood pressure were reported soon after these pills gained approval. Although OCP doses were subsequently reduced, epidemiologic evidence continued to support a smaller, but significant association between OCPs and hypertension. Given the rising prevalence of hypertension, as well as the adverse effects of cumulative exposure to blood pressure elevations on cardiovascular disease risk, understanding the nature of the association between OCPs and hypertension is important for clinicians and patients to assess the risks and benefits of use, and make individualized decisions regarding contraception. Therefore, this review summarizes the current and historical evidence describing the association between OCP use and blood pressure elevations. Specifically, it identifies the pathophysiologic mechanisms linking OCPs to hypertension risk, describes the magnitude of the association between OCPs and blood pressure elevations, and distinguishes the effects of various OCP types on blood pressure. Finally, it describes current recommendations regarding hypertension and OCP use, as well as identifies strategies, such as over-the-counter OCP prescribing, to safely and equitably improve access to oral contraception.

5.Association Between History of Adverse Pregnancy Outcomes and Coronary Artery Disease

IMPORTANCE

Adverse pregnancy outcomes are recognized risk enhancers for cardiovascular disease, but the prevalence of subclinical coronary atherosclerosis after these conditions is unknown.

OBJECTIVE

To assess associations between history of adverse pregnancy outcomes and coronary artery disease assessed by coronary computed tomography angiography screening.

DESIGN, SETTING, AND PARTICIPANTS

Cross-sectional study of a population-based cohort of women in Sweden (n = 10 528) with 1 or more deliveries in 1973 or later, ascertained via the Swedish National Medical Birth Register, who subsequently participated in the Swedish Cardiopulmonary Bioimage Study at age 50 to 65 (median, 57.3) years in 2013-2018. Delivery data were prospectively collected.

EXPOSURES

Adverse pregnancy outcomes, including preeclampsia, gestational hypertension, preterm delivery, small-for-gestational-age infant, and gestational diabetes. The reference category included women with no history of these exposures.

MAIN OUTCOMES AND MEASURES

Coronary computed tomography angiography indexes, including any coronary atherosclerosis, significant stenosis, noncalcified plaque, segment involvement score of 4 or greater, and coronary artery calcium score greater than 100.

RESULTS

A median 29.6 (IQR, 25.0-34.9) years after first registered delivery, 18.9% of women had a history of adverse pregnancy outcomes, with specific pregnancy histories ranging from 1.4% (gestational diabetes) to 9.5% (preterm delivery). The prevalence of any coronary atherosclerosis in women with a history of any adverse pregnancy outcome was 32.1% (95% CI, 30.0%-34.2%), which was significantly higher (prevalence difference, 3.8% [95% CI, 1.6%-6.1%]; prevalence ratio, 1.14 [95% CI, 1.06-1.22]) compared with reference women. History of gestational hypertension and preeclampsia were both significantly associated with higher and similar prevalence of all outcome indexes. For preeclampsia, the highest prevalence difference was observed for any coronary atherosclerosis (prevalence difference, 8.0% [95% CI, 3.7%-12.3%]; prevalence ratio, 1.28 [95% CI, 1.14-1.45]), and the highest prevalence ratio was observed for significant stenosis (prevalence difference, 3.1% [95% CI, 1.1%-5.1%]; prevalence ratio, 2.46 [95% CI, 1.65-3.67]). In adjusted models, odds ratios for preeclampsia ranged from 1.31 (95% CI, 1.07-1.61) for any coronary atherosclerosis to 2.21 (95% CI, 1.42-3.44) for significant stenosis. Similar associations were observed for history

of preeclampsia or gestational hypertension among women with low predicted cardiovascular risk.

CONCLUSIONS AND RELEVANCE

Among Swedish women undergoing coronary computed tomography angiography screening, there was a statistically significant association between history of adverse pregnancy outcomes and image-identified coronary artery disease, including among women estimated to be at low cardiovascular disease risk. Further research is needed to understand the clinical importance of these associations.

6. Women Still at Higher Risk for Adverse Outcomes After CABG

Women have a significantly higher risk for adverse outcomes following coronary artery bypass graft surgery, with no significant change in risk from 2011 to 2020, according to a study published online March 1 in *JAMA Surgery*.

Mario Gaudino, M.D., Ph.D., from Weill Cornell Medicine in New York City, and colleagues conducted a retrospective cohort study involving 1,297,204 patients (24.5 percent women) who underwent primary isolated coronary artery bypass from 2011 to 2020 to evaluate trends in outcomes of women.

The researchers found that compared with men, women had higher unadjusted operative mortality (2.8 versus 1.7 percent) and overall unadjusted incidence of the composite of operative mortality and morbidity (22.9 versus 16.7 percent). From 2011 to 2020, the attributable risk of female sex for operative mortality varied from 1.28 to 1.41. For the composite of operative mortality and morbidity, the attributable risk of female sex was 1.08 in both 2011 and 2020.

"We found that women had higher risk of operative mortality and postoperative complications after CABG compared with men and that the excess risk in women was essentially unchanged over the last decade," the authors write. "We did not observe a significant decrease in the operative risk for women undergoing CABG in the United States between 2011 and 2020."

7. Sex Differences Seen in Vascular Response to Mental Stress

For women, peripheral microvascular dysfunction in response to mental stress is associated with adverse cardiovascular events, according to a study published online March 1 in *Atherosclerosis, Thrombosis, and Vascular Biology* to coincide with the American Heart Association Epidemiology and Prevention/Lifestyle and

Cardiometabolic Health 2023 Scientific Sessions, held from Feb. 28 to March 3 in Boston.

Samaah Sullivan, Ph.D., from The University of Texas Health Science Center in Houston, and colleagues prospectively followed 263 individuals who had been hospitalized for a myocardial infarction in the previous eight months for five years. Microvascular and endothelial function were measured before and 30 minutes after a public-speaking mental stress task. The association between vascular response to stress and major adverse cardiovascular events (MACE) was examined.

Overall, 64 patients had 141 adverse cardiovascular events (first and repeated) during a median follow-up of 4.3 years. The researchers found that among women, worse microvascular response to stress was associated with an increased risk for MACE (hazard ratio, 1.50 for each standard deviation decrease in the reactive hyperemia index). An increased risk for MACE was also seen in association with worse transient endothelial dysfunction response to stress (hazard ratio, 1.35 for each standard deviation decrease in flow-mediated dilation), with a similar association observed among men and women.

"These findings support the importance of psychological stress as a risk factor for women with coronary heart disease and suggest that a microvascular phenomenon may underlie this effect," the authors write.

8. Disparities Persist in CVD Mortality, Despite Overall Decline

Rural counties and counties with a higher percentage of Black residents continue to experience higher cardiovascular disease (CVD) mortality despite overall declines in CVD mortality, according to a study published in the Jan. 17 issue of the *Journal of the American Heart Association*.

Heejung Son, Ph.D., from University of Georgia in Athens, and colleagues used data from the Agency for Healthcare Research and Quality to identify 17 key social determinants of health factors (including rural-urban status, county racial composition, income, food, and housing status) and linked them with CVD mortality data from the Interactive Atlas of Heart Disease and Stroke at the U.S. Centers for Disease Control and Prevention for 3,142 counties from 2009 to 2018.

The researchers found that during the 10-year period, CVD mortality declined at an annual rate of 1.08 deaths per 100,000 people. However, CVD mortality rates were consistently higher among rural counties and counties with a higher percentage of Black residents versus urban counties and counties with a lower

percentage of Black residents. During the last decade, there was no significant change observed in the rural-urban CVD mortality gap, although the association between the percentage of Black residents and CVD mortality showed a significant decline over time.

“We need to be thinking outside of the box,” a coauthor said in a statement. “This study presents evidence for stronger interventions related to housing, income support and food security. We need to be proactive instead of waiting for people to get sick to provide medical care.”

9. Nonacceptance of Statin Recommendation Common, Especially for Women

For patients at high cardiovascular risk, nonacceptance of a statin therapy recommendation is common, especially among women, according to a study published online Feb. 28 in *JAMA Network Open*.

C. Justin Brown, Pharm.D., from Brigham and Women's Hospital in Boston, and colleagues examined sex disparities in nonacceptance of statin therapy in a retrospective cohort study involving statin-naive patients with atherosclerotic cardiovascular disease, diabetes, or low-density lipoprotein (LDL) cholesterol levels of 190 mg/dL or more treated between Jan. 1, 2000, and Dec. 31, 2018.

The researchers found that 21.9 percent of the 24,212 study patients (50.8 percent women) did not accept the initial recommendation of statin therapy. Nonacceptance was more common among women than men (24.1 versus 19.7 percent) and was similarly high in all subgroups stratified by comorbidities. Female sex was associated with lower odds of statin therapy acceptance in a multivariable analysis (odds ratio, 0.82). An LDL cholesterol level of less than 100 mg/dL was achieved during a median of 1.5 versus 4.4 years by those who did versus did not accept a statin therapy recommendation. Nonacceptance of statin therapy was associated with longer time to achieve an LDL cholesterol level less than 100 mg/dL in a multivariable analysis adjusted for demographic characteristics and comorbidities (hazard ratio, 0.57).

"Further research is needed to identify the reasons why patients do not accept statin therapy recommendations and the reasons for the higher rates of this important clinical phenomenon among women," the authors write.

10. Association of Hypertensive Disorders of Pregnancy With Future Cardiovascular Disease

OBJECTIVE

To investigate the association of HDPs with multiple cardiovascular diseases.

DESIGN, SETTING, AND PARTICIPANTS

A genome-wide genetic association study using mendelian randomization (MR) was performed from February 16 to March 4, 2022. Primary analysis was conducted using inverse-variance-weighted MR. Mediation analyses were performed using a multivariable MR framework. All studies included patients predominantly of European ancestry. Female-specific summary-level data from FinnGen (sixth release).

EXPOSURES

Uncorrelated (r2<0.001) single-nucleotide variants (SNVs) were selected as instrumental variants from the FinnGen consortium summary statistics for exposures of any HDP, gestational hypertension, and preeclampsia or eclampsia.

MAIN OUTCOMES AND MEASURES

Genetic association estimates for outcomes were extracted from genome-wide association studies of 122 733 cases for coronary artery disease, 34 217 cases for ischemic stroke, 47 309 cases for heart failure, and 60 620 cases for atrial fibrillation.

RESULTS

Genetically predicted HDPs were associated with a higher risk of coronary artery disease (odds ratio [OR], 1.24; 95% CI, 1.08-1.43; P = .002); this association was evident for both gestational hypertension (OR, 1.08; 95% CI, 1.00-1.17; P = .04) and preeclampsia/eclampsia (OR, 1.06; 95% CI, 1.01-1.12; P = .03). Genetically predicted HDPs were also associated with a higher risk of ischemic stroke (OR, 1.27; 95% CI, 1.12-1.44; P = 2.87 × 10-4). Mediation analysis revealed a partial attenuation of the effect of HDPs on coronary artery disease after adjustment for systolic blood pressure (total effect OR, 1.24; direct effect OR, 1.10; 95% CI, 1.02-1.08; P = .02) and type 2 diabetes (total effect OR, 1.24; direct effect OR, 1.16; 95% CI, 1.04-1.29; P = .008). No associations were noted between genetically predicted HDPs and heart failure (OR, 0.97; 95% CI, 0.76-1.23; P = .79) or atrial fibrillation (OR, 1.11; 95% CI, 0.65-1.88; P = .71).

CONCLUSIONS AND RELEVANCE

The findings of this study provide genetic evidence supporting an association between HDPs and higher risk of coronary artery disease and stroke, which is only partially mediated by cardiometabolic factors. This supports classification of HDPs as risk factors for cardiovascular disease.

11. Pregnancy Outcomes and Vaccine Effectiveness During the Period of Omicron Predominance

BACKGROUND

In 2021, we showed an increased risk associated with COVID-19 in pregnancy. Since then, the SARS-CoV-2 virus has undergone genetic mutations. We aimed to examine the effects on maternal and perinatal outcomes of COVID-19 during pregnancy, and evaluate vaccine effectiveness, when omicron (B.1.1.529) was the variant of concern.

METHODS

INTERCOVID-2022 is a large, prospective, observational study, involving 41 hospitals across 18 countries. Each woman with real-time PCR or rapid test, laboratory-confirmed COVID-19 in pregnancy was compared with two unmatched women without a COVID-19 diagnosis who were recruited concomitantly and consecutively in pregnancy or at delivery. Mother and neonate dyads were followed until hospital discharge. Primary outcomes were maternal morbidity and mortality index (MMMI), severe neonatal morbidity index (SNMI), and severe perinatal morbidity and mortality index (SPMMI). Vaccine effectiveness was estimated, adjusted by maternal risk profile.

FINDINGS

We enrolled 4618 pregnant women from Nov 27, 2021 (the day after WHO declared omicron a variant of concern), to June 30, 2022: 1545 (33%) women had a COVID-19 diagnosis (median gestation 36·7 weeks [IQR 29·0-38·9]) and 3073 (67%) women, with similar demographic characteristics, did not have a COVID-19 diagnosis. Overall, women with a diagnosis had an increased risk for MMMI (relative risk [RR] 1·16 [95% CI 1·03-1·31]) and SPMMI (RR 1·21 [95% CI 1·00-1·46]). Women with a diagnosis, compared with those without a diagnosis, also had increased risks of SNMI (RR 1·23 [95% CI 0·88-1·71]), although the lower bounds of the 95% CI crossed unity. Unvaccinated women with a COVID-19 diagnosis had a greater risk of MMMI (RR 1·36 [95% CI 1·12-1·65]). Severe COVID-19 symptoms in the total sample increased the risk of severe maternal complications (RR 2·51 [95% CI 1·84-3·43]), perinatal complications (RR 1·84 [95% CI 1·02-3·34]), and referral, intensive care unit (ICU) admission, or death

(RR 11·83 [95% CI 6·67-20·97]). Severe COVID-19 symptoms in unvaccinated women increased the risk of MMMI (RR 2·88 [95% CI 2·02-4·12]) and referral, ICU admission, or death (RR 20·82 [95% CI 10·44-41·54]). 2886 (63%) of 4618 total participants had at least a single dose of any vaccine, and 2476 (54%) of 4618 had either complete or booster doses. Vaccine effectiveness (all vaccines combined) for severe complications of COVID-19 for all women with a complete regimen was 48% (95% CI 22-65) and 76% (47-89) after a booster dose. For women with a COVID-19 diagnosis, vaccine effectiveness of all vaccines combined for women with a complete regimen was 74% (95% CI 48-87) and 91% (65-98) after a booster dose.

INTERPRETATION

COVID-19 in pregnancy, during the first 6 months of omicron as the variant of concern, was associated with increased risk of severe maternal morbidity and mortality, especially among symptomatic and unvaccinated women. Women with complete or boosted vaccine doses had reduced risk for severe symptoms, complications, and death. Vaccination coverage among pregnant women remains a priority.

12. Effect of Maternal mRNA COVID-19 Vaccination During Pregnancy on Delta or Omicron Infection and Hospital Admission in Infants

OBJECTIVE

To estimate the effectiveness of maternal mRNA covid-19 vaccination during pregnancy against delta and omicron severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and hospital admission in infants.

DESIGN

Test negative design study.

SETTING

Community and hospital testing in Ontario, Canada.

PARTICIPANTS

Infants younger than six months of age, born between 7 May 2021 and 31 March 2022, who were tested for SARS-CoV-2 between 7 May 2021 and 5 September 2022.

INTERVENTION

Maternal mRNA covid-19 vaccination during pregnancy.

MAIN OUTCOME MEASURES

Laboratory confirmed delta or omicron infection or hospital admission of the infant. Multivariable logistic regression estimated vaccine effectiveness, with adjustments for clinical and sociodemographic characteristics associated with vaccination and infection.

RESULTS

8809 infants met eligibility criteria, including 99 delta cases (4365 controls) and 1501 omicron cases (4847 controls). Infant vaccine effectiveness from two maternal doses was 95% (95% confidence interval 88% to 98%) against delta infection and 97% (73% to 100%) against infant hospital admission due to delta and 45% (37% to 53%) against omicron infection and 53% (39% to 64%) against hospital admission due to omicron. Vaccine effectiveness for three doses was 73% (61% to 80%) against omicron infection and 80% (64% to 89%) against hospital admission due to omicron. Vaccine effectiveness for two doses against infant omicron infection was highest with the second dose in the third trimester (53% (42% to 62%)) compared with the first (47% (31% to 59%)) or second (37% (24% to 47%)) trimesters. Vaccine effectiveness for two doses against infant omicron infection decreased from 57% (44% to 66%) between birth and eight weeks to 40% (21% to 54%) after 16 weeks of age.

CONCLUSIONS

Maternal covid-19 vaccination with a second dose during pregnancy was highly effective against delta and moderately effective against omicron infection and hospital admission in infants during the first six months of life. A third vaccine dose bolstered protection against omicron. Effectiveness for two doses was highest with maternal vaccination in the third trimester, and effectiveness decreased in infants beyond eight weeks of age.

12. Outcomes Following Delivery in Pregnant and Postpartum Patients With Severe COVID-19 Pneumonitis in ICUs in Israel

BACKGROUND

A key unresolved controversy in severe COVID-19 pneumonitis in pregnancy is the optimum timing of delivery and whether delivery improves or worsens maternal outcomes. We aimed to assess clinical data on every intensive care unit (ICU) day for pregnant and postpartum women admitted to the ICU with COVID-19, with a particular focus on the days preceding and following delivery.

METHODS

In this multicentre, nationwide, prospective and retrospective cohort study, we evaluated all pregnant women who were admitted to an ICU in Israel with severe COVID-19 pneumonitis from the 13th week of gestation to the 1st week postpartum. We excluded pregnant patients in which the ICU admission was unrelated to severe COVID-19 pneumonitis. We assessed maternal and neonatal outcomes and longitudinal clinical and laboratory ICU data. The primary overall outcome was maternal outcome (worst of the following: no invasive positive pressure ventilation [IPPV], use of IPPV, use of extracorporeal membrane oxygenation [ECMO], or death). The primary longitudinal outcome was Sequential Organ Failure Assessment (SOFA) score, and the secondary longitudinal outcome was the novel PORCH (positive end-expiratory pressure [PEEP], oxygenation, respiratory support, chest x-ray, haemodynamic support) score. Patients were classified into four groups: no-delivery (pregnant at admission and no delivery during the ICU stay), postpartum (ICU admission ≥1 day after delivery), delivery-critical (pregnant at admission and receiving or at high risk of requiring IPPV at the time of delivery), or delivery-non-critical (pregnant at admission and not critically ill at the time of delivery).

FINDINGS

From Feb 1, 2020, to Jan 31, 2022, 84 patients were analysed: 34 patients in the no-delivery group, four in postpartum, 32 in delivery-critical, and 14 in delivery-non-critical. The delivery-critical and postpartum groups had worse outcomes than the other groups: 26 (81%) of 32 patients in the delivery-critical group and four (100%) of four patients in the postpartum group required IPPV; 12 (38%) and three (75%) patients required ECMO, and one (3%) and two (50%) patients died, respectively. The delivery-non-critical and no-delivery groups had far better outcomes than other groups: six (18%) of 34 patients and two (14%) of 14 patients required IPPV, respectively; no patients required ECMO or died. Oxygen saturation (SpO_2), SpO_2 to fraction of inspired oxygen (FiO_2) ratio (S/F ratio), partial pressure of arterial oxygen to FiO_2 ratio (P/F ratio), ROX index (S/F ratio divided by respiratory rate), and SOFA and PORCH scores were all highly predictive for adverse maternal outcome ($p<0{\cdot}0001$). The delivery-critical group deteriorated on the day of delivery, continued to deteriorate throughout the ICU stay, and took longer to recover (ICU duration, Mantel-Cox $p<0{\cdot}0001$), whereas the delivery-non-critical group improved rapidly following delivery. The day of delivery was a significant covariate for PORCH ($p<0{\cdot}0001$) but not SOFA ($p=0{\cdot}09$) scores.

INTERPRETATION

In patients who underwent delivery during their ICU stay, maternal outcome deteriorated following delivery among those defined as critical compared with non-critical patients, who improved following delivery. Interventional delivery should be considered for maternal indications before patients deteriorate and require mechanical ventilation.

13. Optimizing Prepregnancy CV Health to Improve Outcomes in Pregnant and Postpartum Women and Offspring

This scientific statement summarizes the available preclinical, epidemiological, and clinical trial evidence that supports the contributions of prepregnancy (and interpregnancy) cardiovascular health to risk of adverse pregnancy outcomes and cardiovascular disease in birthing individuals and offspring. Unfavorable cardiovascular health, as originally defined by the American Heart Association in 2010 and revised in 2022, is prevalent in reproductive-aged individuals. Significant disparities exist in ideal cardiovascular health by race and ethnicity, socioeconomic status, and geography. Because the biological processes leading to adverse pregnancy outcomes begin before conception, interventions focused only during pregnancy may have limited impact on both the pregnant individual and offspring. Therefore, focused attention on the prepregnancy period as a critical life period for optimization of cardiovascular health is needed. This scientific statement applies a life course and intergenerational framework to measure, modify, and monitor prepregnancy cardiovascular health. All clinicians who interact with pregnancy-capable individuals can emphasize optimization of cardiovascular health beginning early in childhood. Clinical trials are needed to investigate prepregnancy interventions to comprehensively target cardiovascular health. Beyond individual-level interventions, community-level interventions must include and engage key stakeholders (eg, community leaders, birthing individuals, families) and target a broad range of antecedent psychosocial and social determinants. In addition, policy-level changes are needed to dismantle structural racism and to improve equitable and high-quality health care delivery because many reproductive-aged individuals have inadequate, fragmented health care before and after pregnancy and between pregnancies (interpregnancy). Leveraging these opportunities to target cardiovascular health has the potential to improve health across the life course and for subsequent generations.

14. Worse Cardiac Outcomes Persist for Women: What's the Problem?

Two new studies conclude with the same old messages — women are less likely than men to receive guideline-directed care for acute chest pain and are at higher risk for poor outcomes after bypass surgery.

In one report looking at evaluation of acute chest pain, women were less likely to receive analgesia, 12-lead electrocardiogram, or review by emergency department (ED) clinicians within target times, said Dion Stub, MBBS, PhD, of The Alfred Hospital, Melbourne, Australia. Stub is the principal investigator of the study, published online March 6 in the *Journal of the American College of Cardiology*.

There were also "concerning signals which align with Australian and international studies that mortality was higher for women diagnosed with ST-segment elevation myocardial infarction," Stub told *theheart.org | Medscape Cardiology*.

The second study, looking at outcomes after coronary artery bypass grafting (CABG), published online March 1 in *JAMA Surgery*, "reinforced what we've known known for decades," said lead author Mario Gaudino, MD, PhD of Weill Cornell Medicine in New York City. Operative mortality was significantly higher among women than men, as was a composite of mortality and other adverse outcomes.

"I was hoping to find something different," Gaudino told *theheart.org | Medscape Cardiology*. "The surgical community would like to believe that with the overall improvement in surgical techniques the gap in outcome between the sexes would just disappear. Unfortunately, that's not the case."

"Substantial" Care Differences

To assess sex differences in care for chest pain from emergency medical service (EMS) contact through discharge, Stub and colleagues analyzed data from 256,901 adults (mean age, 61.6 years; 50.3% women) attended by EMS for acute undifferentiated chest pain in Victoria, Australia, from 2015 to 2019.

15. **Sex and age as predictors of health-related quality of life change in Phase II cardiac rehabilitation**

Aims
Cardiac rehabilitation (CR) not only improves cardiovascular outcomes, but also health-related quality of life (HRQOL). Unfortunately, CR is still underutilized, especially among women and older patients. Aim of this study was to highlight age- and sex-specific effects of inpatient CR on HRQOL.
Methods and results
From 2012 to 2018, 18 459 patients were prospectively assessed in six Swiss CR clinics. Of these, we retrospectively analysed a final sample of 8286 patients with a mean (standard deviation) age of 67.8 (11.3) in men and 72.2 (11.3) in women. HRQOL was measured at CR entry and discharge. In multivariable analyses, sex- and age-specific changes in HRQOL throughout CR were estimated, adjusting for baseline HRQOL and clinical characteristics. Participants of both sexes improved significantly ($P < 0.001$) in all domains of HRQOL during CR. Women reported significantly lower social ($P < 0.001$) and emotional ($P < 0.001$) HRQOL than men at CR entry. Female sex predicted greater improvement in social ($F = 19.63$, $P < 0.001$), emotional ($F = 27.814$, $P < 0.001$), and physical HRQOL ($F = 20.473$, $P < 0.001$). In a subgroup of $n = 2632$ elderly patients (>75 years), female sex predicted greater changes in emotional ($F = 15.738$, $P < 0.001$) and physical ($F = 6.295$, $P = 0.012$), but not in social HRQOL.
Conclusion
Women report poorer HRQOL at CR entry compared with men, but in turn particularly benefit from CR in this regard. Our results indicate that sex- and age-specific needs of patients should be considered.

16. Maternal Exposure to PM2.5 and the Risk of Congenital Heart Defects

BACKGROUND

Evidence remains limited about the association of maternal exposure to ambient fine particulate matter (airborne particles with an aerodynamic diameter ≤2.5 μm [$PM_{2.5}$]) with fetal congenital heart defects (CHDs) in highly polluted regions, and few studies have focused on preconception exposure.

METHODS

Using a nationwide surveillance-based case-control design in China, we examined the association between maternal exposure to $PM_{2.5}$ during periconception (defined as 3 months before conception until 3 months into

pregnancy) and risk of CHD in offspring. The study included 1 434 998 births involving 7335 CHDs from 2014 through 2017 on the basis of the National Population-Based Birth Defects Surveillance System, covering 30 provinces, municipalities, or municipal districts in China. We assigned maternal $PM_{2.5}$ exposure during the periconception period to each participant using satellite-based $PM_{2.5}$ concentrations at 1-km spatial resolution. Multilevel logistic regression models were used to calculate the multivariable-adjusted odds ratio and 95% CI for CHDs in offspring associated with maternal $PM_{2.5}$ exposure, and the exposure-response association was investigated using restricted cubic spline analysis. Subgroup or sensitivity analyses were conducted to identify factors that may modify the association.

RESULTS

The average maternal exposure to $PM_{2.5}$ levels across all participants was 56.51 $\mu g/m^3$ (range, 10.95 to 182.13 $\mu g/m^3$). For each 10 $\mu g/m^3$ increase in maternal $PM_{2.5}$ exposure, the risk of CHDs in offspring was increased by 2% (odds ratio, 1.02 [95% CI, 1.00 to 1.05]), and septal defect was the most influenced subtype (odds ratio, 1.04 [95% CI, 1.01 to 1.08]). The effect of $PM_{2.5}$ on CHD risk was more pronounced during the preconception period. Mothers <35 years of age, those living in northern China, and those living in low-income areas were more susceptible to $PM_{2.5}$ exposure than their counterparts (all $P<0.05$). $PM_{2.5}$ exposure showed a linear association with total CHDs or specific CHD types.

CONCLUSIONS

High maternal $PM_{2.5}$ exposure, especially during the preconception period, increases risk of certain types of CHD in offspring. These findings are useful for CHD prevention and highlight the public health benefits of improving air quality in China and other highly polluted regions.

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18. **U-shaped relationship between apolipoprotein A1 levels and mortality risk in men and women**

Background
Apolipoprotein A1 (ApoA1) is the principal protein component of high-density lipoprotein (HDL). Although low HDL cholesterol (HDL-C) levels are known to be associated with greater cardiovascular risk, recent studies have also shown heightened mortality risk at very high HDL-C levels.
Aims
To investigate the sex-specific association between elevated ApoA1 levels and adverse outcomes, and their genetic basis.
Methods
A prospective cohort study of United Kingdom Biobank participants without coronary artery disease at enrollment was performed. The primary exposure was serum ApoA1 levels. The primary and secondary outcome measures were cardiovascular and all-cause death, respectively.
Results
In 402 783 participants followed for a median of 12.1 years, there was a U-shaped relationship between ApoA1 levels and both cardiovascular as well as all-cause mortality, after adjustment for traditional cardiovascular risk factors. Individuals in the highest decile of ApoA1 levels (1.91–2.50 g/L) demonstrated higher cardiovascular (HR 1.21, 95% CI 1.07–1.37, $P < 0.0022$) and all-cause mortality (HR 1.14, 95% CI 1.07–1.21, $P < 0.0001$) compared with those within the lowest risk eighth decile (1.67–1.75 g/L). The U-shaped relationship was present in both sexes, though more pronounced in men. Sensitivity analyses showed that cardiovascular mortality rates were higher in those with greater alcohol intake ($P < 0.004$). Adjustment for polygenic variation associated with higher ApoA1 levels did not attenuate the effect of very high ApoA1 levels on mortality. In the sub-group with very elevated HDL-C levels (> 80 mg/dL in men, > 100 mg/dL in women), there was no association between ApoA1 levels and mortality.
Conclusion
Both very low and very elevated ApoA1 levels are associated with higher cardiovascular and all-cause mortality.

19. Association Between Adverse Pregnancy Outcomes and Long-Term Risk of Ischemic Heart Disease in Mothers

OBJECTIVE

To examine the associations between five major adverse pregnancy outcomes and long term risks of ischemic heart disease in mothers.

DESIGN

National cohort study.

SETTING

Sweden.

PARTICIPANTS

All 2 195 266 women with a first singleton delivery in Sweden during 1973-2015.

MAIN OUTCOME MEASURES

The main outcome measure was incidence of ischemic heart disease from delivery to 2018, identified from nationwide inpatient and outpatient diagnoses. Cox regression was used to calculate hazard ratios for ischemic heart disease associated with preterm delivery, small for gestational age, pre-eclampsia, other hypertensive disorders of pregnancy, and gestational diabetes, adjusting for other adverse pregnancy outcomes and maternal factors. Co-sibling analyses assessed for confounding by shared familial (genetic and environmental) factors.

RESULTS

During 53.6 million person years of follow-up, ischemic heart disease was diagnosed in 83 881 (3.8%) women. All five adverse pregnancy outcomes were independently associated with increased risk of ischemic heart disease. In the 10 years after delivery, adjusted hazard ratios for ischemic heart disease associated with specific adverse pregnancy outcomes were 2.09 (95% confidence interval 1.77 to 2.46) for other hypertensive disorders of pregnancy, 1.72 (1.55 to 1.90) for preterm delivery, 1.54 (1.37 to 1.72) for pre-eclampsia, 1.30 (1.09 to 1.56) for gestational diabetes, and 1.10 (1.00 to 1.21) for small for gestational age. The hazard ratios remained significantly increased even 30-46 years after delivery: 1.47 (1.30 to 1.66) for other hypertensive disorders of pregnancy, 1.40 (1.29 to 1.51) for gestational diabetes, 1.32 (1.28 to 1.36) for pre-eclampsia, 1.23 (1.19 to 1.27) for preterm delivery, and 1.16 (1.13 to 1.19) for small for

gestational age. These findings were only partially (<45%) explained by shared familial (genetic or environmental) factors. Women who experienced multiple adverse pregnancy outcomes showed further increases in risk (eg, <10 years after delivery, adjusted hazard ratios associated with 1, 2, or ≥3 adverse pregnancy outcomes were 1.29 (1.19 to 1.39), 1.80 (1.59 to 2.03), and 2.26 (1.89 to 2.70), respectively)).

CONCLUSIONS

In this large national cohort, women who experienced any of five major adverse pregnancy outcomes showed an increased risk for ischemic heart disease up to 46 years after delivery. Women with adverse pregnancy outcomes should be considered for early preventive evaluation and long term risk reduction to help prevent the development of ischemic heart disease.

20. Long-Term Cardiometabolic Health in People Born After Assisted Reproductive Technology

AIMS

To examine associations of assisted reproductive technology (ART) conception (vs. natural conception: NC) with offspring cardiometabolic health outcomes and whether these differ with age.

METHODS AND RESULTS

Differences in systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), lipids, and hyperglycaemic/insulin resistance markers were examined using multiple linear regression models in 14 population-based birth cohorts in Europe, Australia, and Singapore, and results were combined using meta-analysis. Change in cardiometabolic outcomes from 2 to 26 years was examined using trajectory modelling of four cohorts with repeated measures. 35 938 (654 ART) offspring were included in the meta-analysis. Mean age ranged from 13 months to 27.4 years but was <10 years in 11/14 cohorts. Meta-analysis found no statistical difference (ART minus NC) in SBP (-0.53 mmHg; 95% CI:-1.59 to 0.53), DBP (-0.24 mmHg; -0.83 to 0.35), or HR (0.02 beat/min; -0.91 to 0.94). Total cholesterol (2.59%; 0.10-5.07), HDL cholesterol (4.16%; 2.52-5.81), LDL cholesterol (4.95%; 0.47-9.43) were statistically significantly higher in ART-conceived vs. NC offspring. No statistical difference was seen for triglycerides (TG), glucose, insulin, and glycated haemoglobin. Long-term follow-up of 17 244 (244 ART) births identified statistically significant associations between ART and

lower predicted SBP/DBP in childhood, and subtle trajectories to higher SBP and TG in young adulthood; however, most differences were not statistically significant.

CONCLUSION

These findings of small and statistically non-significant differences in offspring cardiometabolic outcomes should reassure people receiving ART. Longer-term follow-up is warranted to investigate changes over adulthood in the risks of hypertension, dyslipidaemia, and preclinical and clinical cardiovascular disease.

21. **Percutaneous intervention of severe native coarctation of the aorta presenting in pregnancy: a case report**

Background

Coarctation of the aorta (CoA) is one of the more common congenital heart defects affecting up to 5% of patients with congenital heart disease. Pregnant patients with unrepaired or severe re-coarctation are considered to be modified World Health Organisation (mWHO) IV, have the highest risk of maternal mortality and morbidity. The management of unrepaired CoA during pregnancy is influenced by a variety of factors which include the extent of the coarctation and coarctation characteristics, but due to paucity of data, it largely relies on expert opinion.

Case summary

A 27 year old multi-gravid woman underwent successful percutaneous stent implantation for severe native CoA due to maternal resistant hypertension and foetal cardiac compromise on echocardiography. After intervention, the remainder of her pregnancy was uneventful with improved arterial hypertension control. The foetal cardiac structures, namely left ventricular size, improved after intervention. This case demonstrates the importance of CoA intervention during pregnancy to optimise both maternal and foetal outcome.

Conclusion

Coarctation of the aorta should be considered in pregnant women with poorly controlled hypertension. This case also highlights that, despite associated risks, percutaneous intervention can lead to improved maternal haemodynamics and fetal growth.

22. **Sex-related characteristics and short-term outcomes of patients undergoing transcatheter tricuspid valve intervention for tricuspid regurgitation**

Aims

The impact of sexuality in patients with significant tricuspid regurgitation (TR) undergoing transcatheter tricuspid valve intervention (TTVI) is unknown. The aim of this study was to investigate sex-specific outcomes in patients with significant TR treated with TTVI vs. medical therapy alone.

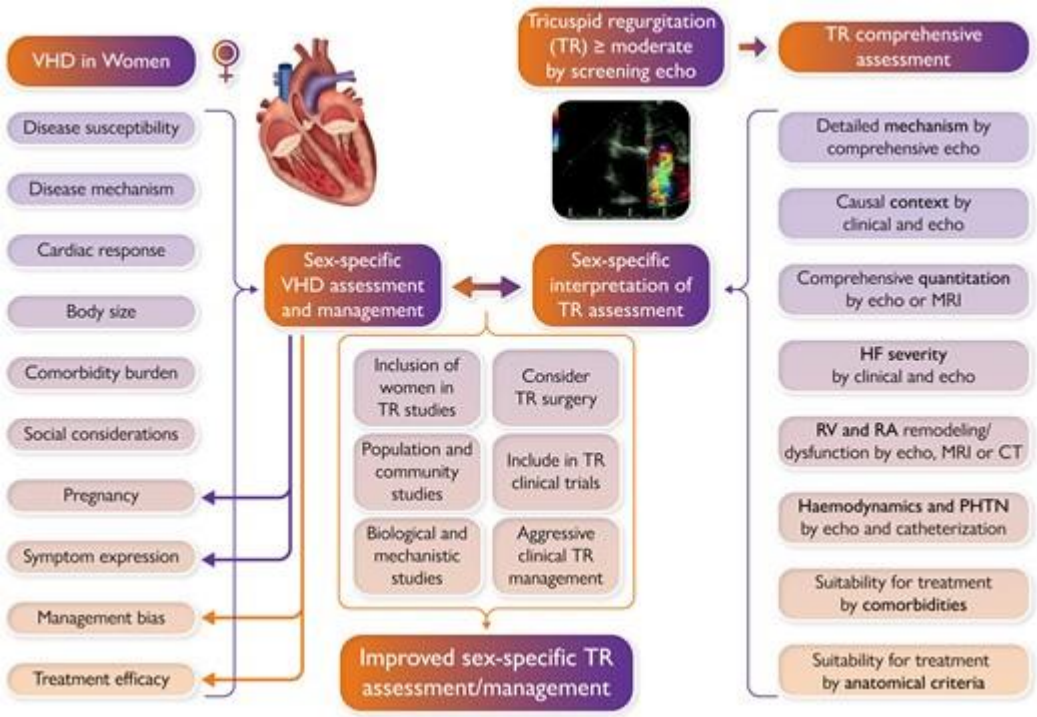
Methods and results

The Transcatheter Tricuspid Valve Therapies (TriValve) registry collected data on patients with significant TR from 24 centres who underwent TTVI from 2016 to 2021. A control cohort was formed by medically managed patients with ≥severe isolated TR diagnosed in 2015–18. The primary endpoint was freedom from all-cause mortality. Secondary endpoints were heart failure (HF) hospitalization, New York Heart Association (NYHA) functional status, and TR severity. One-year outcomes were assessed for the TriValve cohort and compared with the control cohort with the inverse probability of treatment weighting (IPTW). A total of 556 and 2072 patients were included from the TriValve and control groups, respectively. After TTVI, there was no difference between women and men in 1-year freedom from all-cause mortality 80.9% vs. 77.9%, $P = 0.56$, nor in HF hospitalization ($P = 0.36$), NYHA Functional Classes III and IV ($P = 0.17$), and TR severity >2+ at last follow-up ($P = 0.42$). Multivariable Cox-regression weighted by IPTW showed improved 1-year survival after TTVI compared with medical therapy alone in both women (adjusted hazard ratio 0.45, 95% confidence interval 0.23–0.83, $P = 0.01$) and men (adjusted hazard ratio 0.42, 95% confidence interval 0.18–0.89, $P = 0.03$).

Conclusion

After TTVI in high-risk patients, there were no sex-related differences in terms of survival, HF hospitalization, functional status, and TR reduction up to 1 year. The IPTW analysis shows a survival benefit of TTVI over medical therapy alone in both women and men.

23. **Valvular heart diseases in women: facts vs. incantations**



24. Menopausal Hormone Therapy in Women With CVD Risk or Stable CVD

Menopausal hormone therapy (HT) was widely used in the past, but with the publication of seminal primary and secondary prevention trials that reported an excess cardiovascular risk with combined estrogen-progestin, HT use declined significantly. However, over the past 20 years, much has been learned about the relationship between the timing of HT use with respect to age and time since menopause, HT route of administration, and cardiovascular disease risk. Four leading medical societies recommend HT for the treatment of menopausal women with bothersome menopausal symptoms. In this context, this review, led by the American College of Cardiology Cardiovascular Disease in Women Committee, along with leading gynecologists, women's health internists, and endocrinologists, aims to provide guidance on HT use, including the selection of patients and HT formulation with a focus on caring for symptomatic women with cardiovascular disease risk.

25. Sex-Specific Stress Perfusion Cardiac MRI in Suspected Ischemic Heart Disease

BACKGROUND

Cardiovascular disease (CVD) remains the leading cause of mortality in women, but current noninvasive cardiac imaging techniques have sex-specific limitations.

OBJECTIVES

In this study, the authors sought to investigate the effect of sex on the prognostic utility and downstream invasive revascularization and costs of stress perfusion cardiac magnetic resonance (CMR) for suspected CVD.

METHODS

Sex-specific prognostic performance was evaluated in a 2,349-patient multicenter SPINS (Stress CMR Perfusion Imaging in the United States [SPINS] Study) registry. The primary outcome measure was a composite of cardiovascular death and nonfatal myocardial infarction; secondary outcomes were hospitalization for unstable angina or heart failure, and late unplanned coronary artery bypass grafting.

RESULTS

SPINS included 1,104 women (47% of cohort); women had higher prevalence of chest pain (62% vs 50%; P < 0.0001) but lower use of medical therapies. At the 5.4-year median follow-up, women with normal stress CMR had a low annualized rate of primary composite outcome similar to men (0.54%/y vs 0.75%/y, respectively; P = NS). In contrast, women with abnormal CMR were at higher risk for both primary (3.74%/y vs 0.54%/y; P < 0.0001) and secondary (9.8%/y vs 1.6%/y; P < 0.0001) outcomes compared with women with normal CMR. Abnormal stress CMR was an independent predictor for the primary (HR: 2.64 [95% CI: 1.20-5.90]; P = 0.02) and secondary (HR: 2.09 [95% CI: 1.43-3.08]; P < 0.0001) outcome measures. There was no effect modification for sex. Women had lower rates of invasive coronary angiography (ICA; 3.6% vs 7.3%; P = 0.0001) and downstream costs ($114 vs $171; P = 0.001) at 90 days following CMR. There was no effect of sex on diagnostic image quality.

CONCLUSIONS

Stress CMR demonstrated excellent prognostic performance with lower rates of ICA referral in women. Stress CMR should be considered as a first-line

noninvasive imaging tool for the evaluation of women. (Stress CMR Perfusion Imaging in the United States [SPINS] Study [SPINS]; NCT03192891).

26. Comparative Effectiveness of LAAO vs Oral Anticoagulation According to Sex

Randomized clinical trials notoriously enroll patients who may not be representative of patients seen in clinical practice, and enrollment of women in such trials has generally been suboptimal. The latter is true of randomized clinical trials of left atrial appendage occlusion (LAAO) devices in which women comprised only about 30% of the enrolled patients. Therefore, the current study's investigators sought to assess the comparative effectiveness of LAAO devices versus oral anticoagulation by sex in older real-world patients with atrial fibrillation (AF). The study analyzed Medicare claims data from 2015 to 2019 to identify beneficiaries eligible for an LAAO device and examined the results for women and men. Outcomes of interest were all-cause mortality, stroke or systemic embolism, and bleeding. Robust statistical methods were used, including propensity score matching of patients undergoing LAAO device implantation in a 1:1 ratio to patients treated with an oral anticoagulant, and further adjustments were applied for residual differences between the two groups using Cox proportional hazards models. A total of 4085 women who received an LAAO device were matched to 4085 women treated with anticoagulation, and 5378 men who received an LAAO device were matched to 5387 men treated with anticoagulation. The authors found that the LAAO device was associated with a significantly lower risk of mortality for women (HR, 0.509; 95% CI, 0.447–0.580) and men (HR, 0.541; 95% CI, 0.487–0.601) and stroke or systemic embolism (HR, 0.655 for women, and 0.649 for men; $P < .0001$). LAAO recipients had a higher risk of bleeding early after implantation, but the risk was lower after the 6-week periprocedural period elapsed for both sexes. Strengths of the study include providing data on nonclinical trial patients, the large sample size, having a good representation of women, and the rigor of the data analyses. The study also provides helpful information on the type of anticoagulants used by Medicare beneficiaries with a surprisingly high use of vitamin-K antagonists (50%) and the high risk of mortality, stroke, and bleeding in these patients. The authors comprehensively acknowledged the potential limitations of their study especially regarding the fact that no statistical methods can fully adjust for selection bias and confounding factors, the fact that the results may not apply to younger patients, and the lack of data on some important clinical factors including but not limited to AF burden and the extent of cardiac remodeling. The finding of a

lower risk of mortality in the LAAO group is unexpected and likely reflects residual selection bias and confounders, including the closer monitoring of patients in the periprocedural and follow-up periods that may have led to improved outcomes of recipients of the LAAO device. It should be noted, however, that recipients of the LAAO device had a higher burden of comorbidities than patients receiving an anticoagulant, which should have biased the results toward a smaller or no difference in outcomes between the two groups. Importantly, the authors highlight that their findings are associations and do not imply causality. Notwithstanding the limitations of this study, the results are helpful in complementing data from randomized clinical trials in informing shared decision–making encounters with patients, a Centers for Medicare and Medicaid Services requirement prior to implanting LAAO devices in Medicare beneficiaries.

27. Odds of Uncontrolled BP Increased for Black Versus White Women

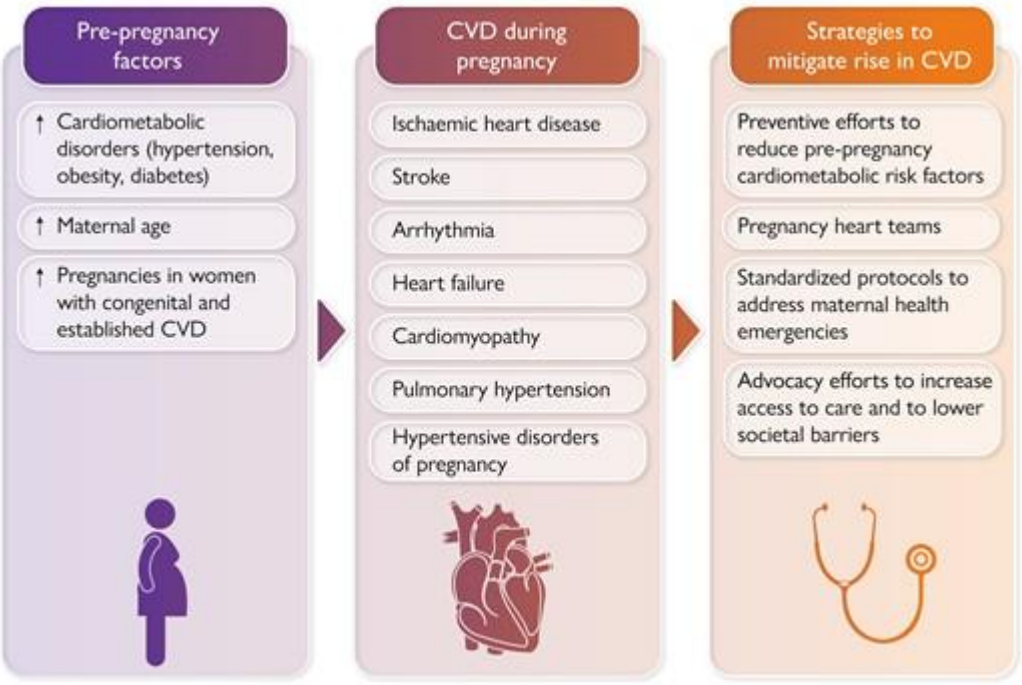
Black women have higher odds of uncontrolled blood pressure (BP) than White women, even after accounting for social determinants of health (SDoH), according to a study published online Feb. 27 in the *Journal of the American Heart Association.*

Claire V. Meyerovitz, from the UMass Chan Medical School in Worcester, Massachusetts, and colleagues examined SDoH and BP control by race and ethnicity among 1,293 women aged 20 to 50 years with hypertension (59.2 percent White, 23.4 percent Black, 15.8 percent Hispanic, and 1.7 percent Asian).

The researchers found that compared with White women, more Hispanic and Black women experienced food insecurity (32 and 25 versus 13 percent). Black women maintained higher odds of uncontrolled BP than White women after adjustment for SDoH, health factors, and modifiable health behavior, while no difference was seen for Asian and Hispanic women.

"Black women have higher odds of uncontrolled hypertension, even when SDoH are controlled for," the authors write. "This potentially indicates a greater role for alternative factors, including racism and discrimination, which have affected daily life and opportunities for generations."

28. **Time to counter rising cardiovascular disease during pregnancy**

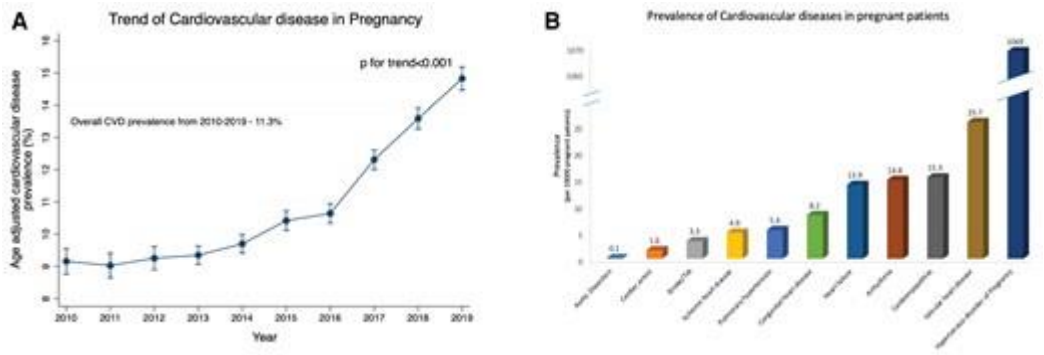


29. **Cardiovascular diseases in pregnancy, congenital heart disease, and arrhythmias: lessons from epidemiology**

This Focus Issue on epidemiology, prevention, and healthcare policies contains the State of the Art Review article '**Artificial intelligence to enhance clinical value across the spectrum of cardiovascular healthcare**' by Simrat Gill from the University of Birmingham in the UK, and colleagues.1 The authors note that artificial intelligence (AI) is increasingly being utilized in healthcare.2–8 This article provides clinicians and researchers with a stepwise foundation for high-value AI that can be applied to a variety of different data modalities. The aim is to improve the transparency and application of AI methods, with the potential to benefit patients in routine cardiovascular care. Following a clear research hypothesis, an AI-based workflow begins with data selection and pre-processing prior to analysis, with the type of data (structured, semi-structured, or unstructured) determining what type of pre-processing steps and machine-learning algorithms are required. Algorithmic and data validation should be performed to ensure the robustness of the chosen methodology, followed by an objective evaluation of performance. Seven case studies are provided to highlight the wide variety of data modalities and clinical questions that can benefit from modern AI techniques, with a focus on applying them to cardiovascular disease management. Despite the growing use of AI, further education for healthcare workers, researchers, and the public is needed to aid understanding of how AI works and to close the existing gap in knowledge. In addition, issues regarding

data access, sharing, and security must be addressed to ensure full engagement by patients and the public. The application of AI within healthcare provides an opportunity for clinicians to deliver a more personalized approach to medical care by accounting for confounders, interactions, and the rising prevalence of multi-morbidity.

Figure 1



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Trend and prevalence of cardiovascular disease in pregnant patients. (*A*) Age-adjusted trend of cardiovascular disease from 2010 to 2019. (*B*) Frequency of specific cardiovascular disease categories.12

Contemporary data on the prevalence, trends, and outcomes of cardiovascular diseases (CVDs) in pregnant women are limited.9–11 In a Fast Track Clinical Research article entitled '**Prevalence, trends, and outcomes of cardiovascular diseases in pregnant patients in the USA: 2010–19**', Monil Majmundar from the University of Kansas Medical Center in the USA, and colleagues aimed to analyse the prevalence, trends, and outcomes of CVD in hospitalized pregnant women in the USA.12 This retrospective population-based cohort study used the Nationwide Readmission Database to identify all hospitalized pregnant patients from 1 January 2010 to 31 December 2019. Data analyses were conducted from January to February 2022. Pregnancy-associated hospitalizations were identified. The main outcomes were the prevalence and trend of CVD in pregnant patients. More than 39 000 000 hospitalized pregnant women were identified: 11.3% exhibited CVD. The annual age-adjusted CVD prevalence increased from 9.2% in 2010 to 14.8% in 2019 ($P < 0.001$). Hypertensive disorder of pregnancy was the most common, and aortic dissection was the least common CVD. The trends of all CVD subtypes increased; however, the trend of valvular heart disease decreased. Age-adjusted in-hospital all-cause mortality was 8.2/10 000 in CVD, but its trend decreased from 8.1/10 000 in 2010 to 6.5/10 000 in 2019

($P < 0.001$). CVD was associated with 15.51 times higher odds of in-hospital all-cause mortality compared with non-CVD patients ($P < 0.001$). CVD was associated with higher 6-week post-partum readmission [odds ratio (OR) 1.97], myocardial infarction (OR 3.04), and stroke (OR 2.66) ($P < 0.001$ for all) (*Figure 1*).

The authors conclude that there is an increasing age-adjusted trend in overall CVD and its subtypes among pregnant patients in the USA from 2010 to 2019. Pregnant patients with CVD have higher odds of in-hospital mortality than those without CVD. However, in-hospital all-cause mortality among patients with and without CVD has decreased over the past 10 years. CVD is associated with higher 6-week post-partum all-cause readmission, myocardial infarction, and stroke rates. The contribution is accompanied by an **Editorial** by Martha Gulati from Cedars Sinai Medical Center in Los Angeles, CA, USA and Anum Minhas from Johns Hopkins University School of Medicine in Baltimore, MD, USA.13 The authors conclude that maternal morbidity and mortality rates in the USA remain the highest of all industrialized nations, with most maternal deaths being preventable. These alarming statistics and disparities in outcomes necessitate an active effort and commitment from the healthcare community and government to urgently address this ongoing crisis.

In a continuously ageing population of patients with congenital heart disease (CHD), understanding the long-term risk of morbidity is crucial.14–16 In a Clinical Research article entitled '**Lifetime risk of comorbidity in patients with simple congenital heart disease: a Danish nationwide study**', Mohamad El-Chouli from the Danish Heart Foundation in Copenhagen, Denmark, and colleagues compare the lifetime risks of developing comorbidities in patients with simple CHD and matched controls.17 Using the Danish nationwide registers spanning from 1977 to 2018, simple CHD cases were defined as isolated atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary stenosis, or patent ductus arteriosus in patients surviving until at least 5 years of age. There were 10 controls identified per case. Reported were absolute lifetime risks and lifetime risk differences (between patients with simple CHD and controls) of incident comorbidities stratified by groups and specific cardiovascular comorbidities. Of the included 17 157 individuals with simple CHD, the largest subgroups were those with ASD (38%) and VSD (34%), and 52% were females. The median follow-up time for patients with CHD was 21.2 years and for controls, 19.8 years. The lifetime risks for the investigated comorbidities were higher and appeared overall at younger ages for simple CHD compared with controls, except for neoplasms and chronic kidney disease. The lifetime risk

difference among the comorbidity groups was highest for neurological disease and pulmonary disease, and, among the specific comorbidities was highest for stroke. The overall risk of stroke in patients with simple CHD was mainly driven by ASD, while the risks of myocardial infarction and heart failure were driven by VSD. The associated lifetime risks of stroke, myocardial infarction, and heart failure in both sexes were smaller in invasively treated patients compared with untreated patients with simple CHD.

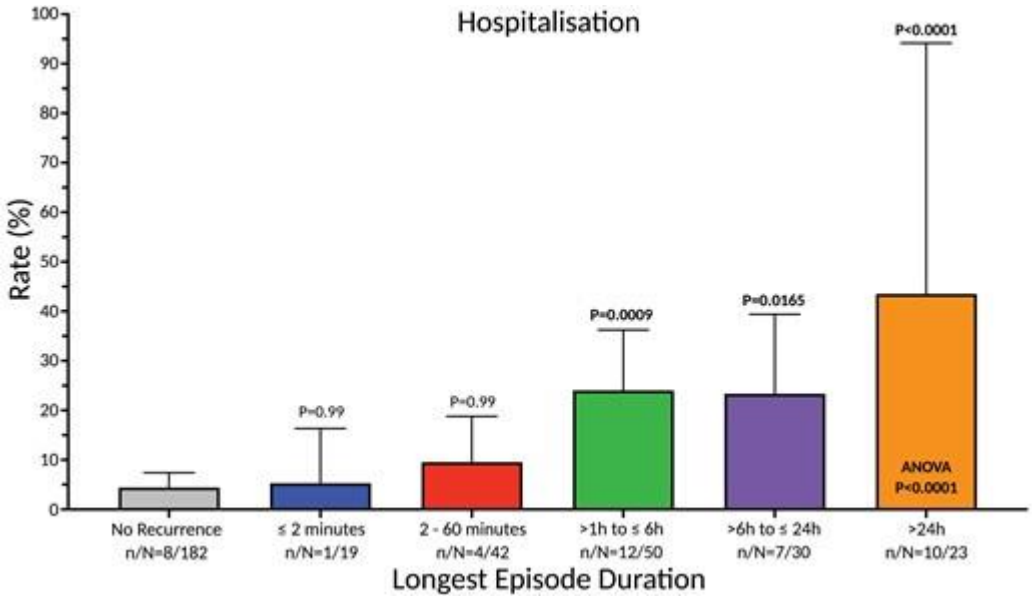
El-Chouli and colleagues conclude that patients with simple CHD have increased lifetime risks of all comorbidities compared with matched controls, except for neoplasms and chronic kidney disease. These findings highlight the need for increased attention towards early management of comorbidity risk factors. The contribution is accompanied by an **Editorial** by Pastora Gallego from the Instituto BioMedicina in Sevilla, Spain.18 Gallego highlights that the authors are to be commended for their important population-based study that provides valuable information on the burden and temporal trends of comorbidities in a large cohort of adults with simple CHD. Addressing comorbidities is a challenge for the healthcare system, requiring partnerships with primary care physicians and non-cardiologist specialists, and educating and teaching patients to self-monitor, communicate their symptoms, and improve their lifestyle. It is essential that we continue to collect accurate data on the outcomes of our treatments that can guide the future management of these patients. This study underscores the need for individualized longitudinal follow-up of simple heart defects, which may often require highly specialized cardiac care under certain circumstances. The data also support the need for prevention, early diagnosis, and treatment of specific and highly prevalent comorbidities in this population to achieve optimal long-term outcomes and quality of life. Further disease-specific research would shed further light on mechanisms of comorbidity risk and inform risk stratification strategies.

The predictors of advanced atrioventricular block are still incompletely known.19,20 In a Clinical Research article entitled '**Type 2 diabetes mellitus and higher rate of complete atrioventricular block: a Danish Nationwide Registry**', Saranda Haxha from the Bispebjerg and Frederiksberg Hospital in Copenhagen, Denmark, and colleagues aimed to determine the association between Type 2 diabetes mellitus (T2DM) and third-degree (complete) atrioventricular block.21 This nationwide nested case–control study included patients older than 18 years, diagnosed with third-degree atrioventricular block between 1 July 1995 and 31 December 2018. Five controls, from the risk set of each case of third-degree atrioventricular block, were matched on age and sex to

fit a Cox regression model with time-dependent exposure and time-dependent covariates. Subgroup analysis was conducted with Cox regression models for each subgroup. The authors identified ~26 000 cases with third-degree atrioventricular block. The mean age was 76 years, and 62% were male. Cases had more T2DM (21% vs. 11%), hypertension (69% vs. 50%), atrial fibrillation (AF; 25% vs. 10%), heart failure (20% vs. 6.3%), and myocardial infarction (19% vs. 9.2%) compared with the control group. In Cox regression analysis, adjusting for comorbidities and atrioventricular nodal blocking agents, T2DM was significantly associated with third-degree atrioventricular block (hazard ratio 1.63). The association remained in several subgroup analyses of diseases also suspected to be associated with third-degree atrioventricular block. There was a significant interaction with comorbidities of interest including hypertension, AF, heart failure, and myocardial infarction.

The authors conclude that in this nationwide study, T2DM is associated with a higher rate of third-degree atrioventricular block compared with matched controls. The association remains independent of atrioventricular nodal blocking agents and other comorbidities known to be associated with third-degree atrioventricular block. This manuscript is accompanied by an **Editorial** by Moshe Rav Acha and Michael Glikson from the Hebrew University in Jerusalem, Israel.22 The authors conclude that an extensive amount of data supports the association of T2DM with atrioventricular block, although it seems to have remained unnoticed until now. Multiple studies suggest that this association is independent of other cardiovascular conventional risk factors and may explain at least part of the increased sudden cardiac death (SCD) among these patients. The pathogenesis of this association is probably multifactorial and mostly still obscure. Nevertheless, this association has an important clinical implication regarding the need to continuously evaluate T2DM patients' conduction system probably by serial ECGs, looking for advanced atrioventricular block. Early diagnosis among these patients might reduce their increased susceptibility to SCD.

Figure 2



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Healthcare utilization as a function of the duration of the longest recorded episode.23

Atrial tachyarrhythmia recurrence ≥30 s remains the primary endpoint of clinical trials; however, this definition has not been correlated with clinical outcomes or pathophysiological processes. In a Clinical Research article entitled '**Healthcare utilization and quality of life for atrial fibrillation burden: the CIRCA-DOSE study**', Jason G. Andrade from the Université de Montréal in Canada, and colleagues sought to determine the atrial tachyarrhythmia duration and burden associated with meaningful clinical outcomes.23 The time and duration of every atrial tachyarrhythmia episode recorded on an implantable cardiac monitor were evaluated. Details of healthcare utilization and quality of life in the year following ablation were prospectively collected. Three hundred and forty-six patients provided >126 000 monitoring days. One-year freedom from recurrence increased with arrhythmia duration thresholds, from 52% to 93% ($P < 0.0001$). Patients with AF recurrence limited to durations ≤1 h had rates of healthcare utilization comparable with those of patients free of recurrence, while patients with AF recurrences lasting >1 h had a relative risk for emergency department consultation of 3.2, hospitalization of 5.3, and repeat ablation of 27. Patients with AF burden of ≤0.1% had rates of healthcare utilization comparable with those of patients free of recurrence, while patients with AF burden of >0.1% had a relative risk for emergency department consultation of 2.4, hospitalization of 6.8, cardioversion of 9.1, and repeat ablation of 21.8. Compared with patients

free of recurrence, the disease-specific quality of life was significantly impaired with AF episode durations >24 h, or AF burdens >0.1% (*Figure 2*).

The authors conclude that AF recurrence, as defined by 30 s of arrhythmia, lacks clinical relevance. AF episode durations >1 h or burdens >0.1% are associated with increased rates of healthcare utilization. The contribution is accompanied by an **Editorial** by Ahmed Al-Kaisey and Jonathan M. Kalman from the University of Melbourne in Australia.24 The authors conclude that these data from a rigorous prospective study provide strong evidence that it is time to discard the 30 s cut-off point, and institute endpoints of clinical relevance.

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

Dr. Crea reports speaker fees from Abbott, Amgen, Astra Zeneca, BMS, Chiesi, Daiichi Sankyo, Menarini outside the submitted work.

With thanks to Amelia Meier-Batschelet, Johanna Huggler, and Martin Meyer for help with compilation of this article.

30. What Is Ambivalent Sexism, and What Are Its Health Effects?

Sexism can take different forms, some of which are disguised as protectiveness and flattery. Nevertheless, sexism, in whatever form, has a negative effect on how women are perceived and treated by others and by themselves. The theory of, and research on, ambivalent sexism, which encompasses attitudes that are overtly negative (hostile sexism) and those that seem subjectively positive but are actually harmful (benevolent sexism), have made substantial contributions to understanding how sexism operates and the consequences it has for women. One review published recently in *Nature Reviews Psychology* summarized the predictors of ambivalent sexism and the impact on women's health.

Various Forms

Sexism is a type of prejudice that specifically ranks women lower than men. Although it can take overtly negative — and in some cases even violent — forms, sexist attitudes toward women may not be overtly negative. Indeed, women will often be described in a more positive light than men. However, the positive descriptions of women tend to be limited to traits linked to empathy (women are sociable and kind), whereas men are described more positively in areas such as

agency and competence, which determine status and power in society (men are brilliant and capable).
The theory of ambivalent sexism accounts for these specific circumstances and postulates that sexism combines antipathy (hostile sexism) with subjective benevolence (benevolent sexism) in its attitude toward women to maintain the dominance that men hold over women.

Sexism and Health

Although women and men can experience sexism, women are more commonly the target of this type of prejudice, despite the perceived progress made in women's rights over the last decade. Because of its pervasiveness, sexism toward women has been conceptualized as a daily "hassle" that may have dire implications for women's mental and physical health.
Despite the lack of consensus on whether to incorporate or even investigate sex and gender differences in treatment paradigms, research investigating social determinants of health has uncovered evidence that women's symptoms are often barely acknowledged or even dismissed by medical professionals (medical sexism). This has inspired research and interventions aimed at reducing the biases displayed by health care professionals, with the goal of reducing sex disparities in healthcare management.

Sexism and Illness

Despite being the main cause of death worldwide in women each year, cardiovascular disease (CVD) in women remains underrecognized, underdiagnosed, and undertreated. For example, in comparing data from the National Health and Nutrition Estimation Survey (NHANES) III (1988-94) and NHANES IV (1999-2002), more postmenopausal women were hypertensive than age-matched men. Moreover, fewer postmenopausal women than men had their blood pressure controlled to goal.
It has been hypothesized that, based on the NHANES data, it's likely that either women are not being treated as aggressively for their CVD, or other mechanisms that are not common in men may contribute to their CVD. The positive association between experiences of sexism and posttraumatic stress disorder, psychological distress, and the frequency of smoking and drinking behavior among women should incite researchers to examine it in more depth as an additional cardiovascular risk factor in women.
Furthermore, cardiovascular warning signs may be detected in women targeted by benevolent and hostile sexism, with heightened cardiovascular reactivity to hostile sexism experiences, but also after benevolent sexism experiences with impaired cardiovascular recovery in returning to baseline functions.

Sexism may also be a notable factor of physical stress, and experiences of benevolent and hostile sexism are associated with an increase in self-reported anxiety and rage, with relatively stronger associations for hostile sexism than for benevolent sexism. Even today we still find it difficult to know how to discriminate between the specific emotional and psychological aftereffects of exposure to various forms of ambivalent sexism, and this will be one of the aims of future research in the field.

31. ACC 2023: Hormone Therapy for People With Gender Dysphoria May Increase Risk for Cardiac Events

Use of hormone therapy for people with gender dysphoria may increase the risk for cardiac events, according to research presented at the annual meeting of the American College of Cardiology together with the World Congress of Cardiology, held from March 4 to 6 in New Orleans.

"Starting hormone replacement therapy or gender-affirming hormone therapy is not a risk-free endeavor, and there are risks as well as benefits with undergoing this therapy. We believe that a thorough review of risks and benefits should be had between a patient and their physician," Ibrahim Ahmed, M.D., of Mercy Catholic Medical Center in Philadelphia, told Elsevier's *PracticeUpdate.*

Ahmed and colleagues performed a retroactive chart review using the 2019 Nationwide Inpatient Sample database to identify adults with a diagnosis of gender dysphoria and use of hormone replacement therapy. They identified a total of 21,335 gender dysphoria patients, of whom 1,675 underwent hormone therapy.

The researchers found that hormone replacement therapy was significantly associated with ischemic stroke (odds ratio [OR], 7.15; 95 percent confidence interval [CI], 2.74 to 18.67; $P < 0.001$), pulmonary embolism (OR, 4.92; 95 percent CI, 2.08 to 11.62; $P < 0.001$), ST elevation myocardial infarction (OR, 5.90; 95 percent CI, 1.07 to 32.42; $P < 0.05$), and non-ST-elevation myocardial infarction (OR, 3.30; 95 percent CI, 1.20 to 9.04; $P < 0.05$). Hormone replacement therapy was not significantly associated with atrial fibrillation (OR, 0.48; 95 percent CI, 0.18 to 1.32; $P = 0.155$), diabetes mellitus (OR, 0.90; 95 percent CI, 0.49 to 1.64; $P = 0.727$), hypertension (OR, 1.23; 95 percent CI, 0.88 to 1.72; $P = 0.217$), hemorrhagic stroke (OR, 2.36; 95 percent CI, 0.51 to 10.98; $P = 0.275$), or systolic heart failure (OR, 1.62; 95 percent CI, 0.72 to 3.69; $P = 0.246$).

Those taking hormone replacement therapy had similar all-cause mortality rates (0.60 versus 0.48 percent; P = 0.7741), mean length of stay (5.71 versus 6.09 days; P = 0.321), and mean total hospitalization charge ($61,011.71 versus $49,930.34; P = 0.598) as the non-hormone replacement therapy cohort.

“There is very little research in patients with gender dysphoria taking hormone replacement therapy, which I believe is contributing to the health disparities that exist in this community,” Ahmed told Elsevier’s *PracticeUpdate*.

He added that future research should focus on the best route of administration for hormone therapy, as some research has shown that oral estrogen confers a higher risk for venous thromboembolism compared with transdermal administration in biologic women. “By studying different routes of administration, we can best choose a route of administration that reduces cardiovascular risks the most,” he concluded.

32. **Sex- and age-specific normal values for automated quantitative pixel-wise myocardial perfusion cardiovascular magnetic resonance**

Aims

Recently developed in-line automated cardiovascular magnetic resonance (CMR) myocardial perfusion mapping has been shown to be reproducible and comparable with positron emission tomography (PET), and can be easily integrated into clinical workflows. Bringing quantitative myocardial perfusion CMR into routine clinical care requires knowledge of sex- and age-specific normal values in order to define thresholds for disease detection. This study aimed to establish sex- and age-specific normal values for stress and rest CMR myocardial blood flow (MBF) in healthy volunteers.

Methods and results

A total of 151 healthy volunteers recruited from two centres underwent adenosine stress and rest myocardial perfusion CMR. In-line automatic reconstruction and post processing of perfusion data were implemented within the Gadgetron software framework, creating pixel-wise perfusion maps. Rest and stress MBF were measured, deriving myocardial perfusion reserve (MPR) and were subdivided by sex and age. Mean MBF in all subjects was 0.62 ± 0.13 mL/g/min at rest and 2.24 ± 0.53 mL/g/min during stress. Mean MPR was 3.74 ± 1.00. Compared with males, females had higher rest (0.69 ± 0.13 vs. 0.58 ± 0.12 mL/g/min, $P < 0.01$) and stress MBF (2.41 ± 0.47 vs. 2.13 ± 0.54 mL/g/min, $P = 0.001$). Stress MBF and MPR showed significant negative

correlations with increasing age ($r = -0.43$, $P < 0.001$ and $r = -0.34$, $P < 0.001$, respectively).

Conclusion

Fully automated in-line CMR myocardial perfusion mapping produces similar normal values to the published CMR and PET literature. There is a significant increase in rest and stress MBF, but not MPR, in females and a reduction of stress MBF and MPR with advancing age, advocating the use of sex- and age-specific reference ranges for diagnostic use.

33. History of Adverse Pregnancy Outcomes Linked to Coronary Artery Disease

There is a significant association between a history of adverse pregnancy outcomes and later image-identified coronary artery disease, according to a study published in the Feb. 7 issue of the *Journal of the American Medical Association*.

Sofia Sederholm Lawesson, M.D., Ph.D., from Linköping University Hospital in Sweden, and colleagues examined the associations between a history of adverse pregnancy outcomes (preeclampsia, gestational hypertension, preterm delivery, small-for-gestational-age infant, and gestational diabetes) and later coronary artery disease assessed by coronary computed tomography angiography screening. Data were included for a population-based cohort of 10,528 women in Sweden with one or more deliveries in 1973 or later who subsequently participated in the Swedish Cardiopulmonary Bioimage Study at age 50 to 65 years from 2013 to 2018.

The researchers found that 18.9 percent of women had a history of adverse pregnancy outcome, with specific pregnancy histories varying from 1.4 percent for gestational diabetes to 9.5 percent for preterm delivery. For women with any adverse pregnancy outcome, the prevalence of any coronary atherosclerosis was 32.1 percent, which was significantly higher than among reference women without a history of adverse pregnancy outcome (prevalence ratio, 1.14). A history of gestational hypertension and preeclampsia were both associated with a similarly increased prevalence of all outcomes. In adjusted models, the odds ratios for preeclampsia ranged from 1.31 to 2.21 for any coronary atherosclerosis to significant stenosis, respectively. Women with low predicted cardiovascular risk had similar associations for a history of preeclampsia or gestational hypertension.

"Our results suggest that the correlation exists even among women with a low expected risk of cardiovascular disease," a coauthor said in a statement. "The study is an important piece of the puzzle in understanding how women with pregnancy complications should be followed-up by their health care provider after pregnancy."

33. Editorial: What Has Sex Got To Do With It?

Atrial fibrillation (AF) is a leading cause of cardiovascular disease worldwide with a projected prevalence to exceed 10 million people by 2050 [1] . Research demonstrates that atrial fibrillation is associated with a higher risk of all-cause mortality, and a significantly higher risk of stroke and cardiac events in women [2] . With trends predicting sex differences in atrial fibrillation associated outcomes, it is reasonable to assume that sex differences may also play an important role on selecting treatments, including percutaneous left atrial appendage occlusion (LAAO) implantation. LAAO implantation has been shown to be a safe alternative for patients with AF who have contraindications to anticoagulation.

34. Few Women on Latin American Journals' Editorial Boards

Women are a minority on the editorial boards of Latin American and Caribbean scientific journals focused on surgery, anesthesiology, and obstetrics and gynecology. "Women held 17% of total editorial board positions in the areas mentioned," wrote the authors of one of the first studies on the subject in Latin America, which recently was published by the *World Journal of Surgery*.

"We arrived at this number by looking at the scientific journals we analyzed," researcher Letícia Nunes Campos, a graduate student affiliated with the Department of Medical Sciences of the University of Pernambuco, Recife, Brazil, explained to *Medscape Medical News*. Campos is coauthor of the study in conjunction with a team of women researchers affiliated with universities in Brazil, Argentina, the United States, Russia, and Canada.

The group analyzed 19 of 25 active journals selected through the Scimago Journal & Country Rank (SJR). SJR is a publicly available portal that includes the scientific indicators of journals and countries, which are developed based on information contained in the Scopus database. The group chose nine scientific journals focused on surgery, three on anesthesiology, and seven on obstetrics and gynecology, all edited in the following five Latin American countries: Brazil, Colombia, Chile, Mexico, and Cuba. A study of the publications' websites yielded 1320 names of editorial board members.

These members were then classified as senior (editors in chief, specialized positions, honorary positions), academic (national editorial board positions, peer reviewers, external academic editorial board positions), and nonacademic role categories (nonacademic positions, administrative positions).

"Our study shows that women had more peer reviewer roles than editorial board positions, and there were no women in honorary roles in Latin America," the authors wrote. This demonstrates the effects of the phenomenon known as the "leaky pipeline," in which the proportion of women decreases substantially at each step up the academic ladder. "Consequently, these gaps affect the representation of women in editorial board positions, as well as their respective academic progress," Campos and researchers Ayla Gerk Rangel, MD, Júlia Loyola Ferreira, MD, and Roseanne Ferreira, MD, told *Medscape*.

The percentage of women per board ranged from 0.0% to 57.1%, and there was a significant difference between the journals for women's representation on the editorial board ($P = .007$). Notably, only one journal board had more than 50% women — *Revista Cubana de Obstetricia y Ginecologia*, a Cuban obstetrics and gynecology journal. Regarding participation, women held fewer academic roles (14.3%, 155/1084) than senior (28.9%, 64/221, $P < .001$) and nonacademic roles (38.4%, 5/13, $P = .042$).

In the subgroup analysis of senior roles, the authors observed that specialized positions, including deputy editor and executive editor, included more women (31.5%, 60/190) than honorary roles (0%, 0/15, $P = .018$). No difference was observed comparing these roles to editors in chief (25%, 4/16).

35. Ectopic Pregnancy Risk and Levonorgestrel-Releasing IUD

Researchers report that use of any levonorgestrel-releasing intrauterine system was associated with a significantly increased risk of ectopic pregnancy, compared with other hormonal contraceptives, in a study published in JAMA.

A national health database analysis headed by Amani Meaidi, MD, PhD, of the Danish Cancer Society Research Center, Cancer Surveillance and Pharmacoepidemiology, in Copenhagen, compared the 13.5-mg with the 19.5-mg and 52-mg dosages of levonorgestrel-releasing intrauterine systems (IUSs).

The hormone content in levonorgestrel-releasing IUSs must be high enough to maintain optimal contraceptive effect but sufficiently low to minimize progestin-related adverse events, Dr. Meaidi and colleagues noted; they advised using the middle dosage of 19.5 mg. All dosages are recommended for contraception, with the highest dosage also recommended for heavy menstrual bleeding.

"If 10,000 women using the hormonal IUD for 1 year were given the 19.5-mg hormonal IUD instead of the 13.5-mg hormonal IUD, around nine ectopic pregnancies would be avoided," Dr. Meaidi said in an interview.
"Ectopic pregnancy is an acknowledged adverse event of hormonal IUD use. Although a rare event, it is a serious one, and a difference in ectopic pregnancy safety between the two low-dose hormonal IUDs would impact my recommendations to women."
The study

Dr. Meaidi's group followed 963,964 women for 7.8 million person-years. For users of levonorgestrel IUS dosages 52 mg, 19.5 mg, and 13.5 mg, and other hormonal contraceptives, the median ages were 24, 22, 22, and 21 years, respectively.
Eligible women were nulliparous with no previous ectopic pregnancy, abdominal or pelvic surgery, infertility treatment, endometriosis, or use of a levonorgestrel IUS. They were followed from Jan. 1, 2001, or their 15th birthday, until July 1, 2021, age 35, pregnancy, death, emigration, or the occurrence of any exclusion criterion.
During the study period, the cohort registered 2,925 ectopic pregnancies, including 35 at 52 mg, 32 at 19.5 mg, and 80 at 13.5 mg of levonorgestrel. For all other types of hormonal contraception, there were 763 ectopic pregnancies.
In terms of adjusted absolute rates of ectopic pregnancy per 10,000 person-years, compared with other hormonal contraceptives (rate = 2.4), these were 7.7 with 52 mg levonorgestrel IUS, 7.1 with 19.5 mg, and 15.7 with 13.5 mg. They translated to comparative differences of 5.3 (95% confidence interval, 1.9-8.7), 4.8 (95% CI, 1.5-8.0), and 13.4 (95% CI, 8.8-18.1), respectively.

36. Mpox Cases Among Cisgender Women and Pregnant Persons — United States, May 11–November 7, 2022

Introduction

Monkeypox (mpox) cases in the 2022 outbreak have primarily occurred among adult gay, bisexual, and other men who have sex with men (MSM); however, other populations have also been affected.[1] To date, data on mpox in cisgender women and pregnant persons have been limited. Understanding transmission in these populations is critical for mpox prevention. In addition, among pregnant persons, *Monkeypox virus* can be transmitted to the fetus during pregnancy or to the neonate through close contact during or after birth.[2–5] Adverse pregnancy

outcomes, including spontaneous abortion and stillbirth, have been reported in previous mpox outbreaks.[3] During May 11–November 7, 2022, CDC and U.S. jurisdictional health departments identified mpox in 769 cisgender women aged ≥15 years, representing 2.7% of all reported mpox cases.† Among cases with available data, 44% occurred in cisgender women who were non-Hispanic Black or African American (Black), 25% who were non-Hispanic White (White), and 23% who were Hispanic or Latino (Hispanic). Among cisgender women with available data, 73% reported sexual activity or close intimate contact as the likely route of exposure, with mpox lesions most frequently reported on the legs, arms, and genitals. Twenty-three mpox cases were reported in persons who were pregnant or recently pregnant§; all identified as cisgender women based on the mpox case report form.¶ Four pregnant persons required hospitalization for mpox. Eleven pregnant persons received tecovirimat, and no adverse reactions were reported. Continued studies on mpox transmission risks in populations less commonly affected during the outbreak, including cisgender women and pregnant persons, are important to assess and understand the impact of mpox on sexual, reproductive, and overall health.

Data on confirmed and probable cases of mpox are electronically reported as part of national case surveillance through a standardized case report form or the National Notifiable Diseases Surveillance System.** Data are collected by health departments and include demographic characteristics, possible exposure routes, and signs and symptoms. CDC analyzed case report data for probable or confirmed†† cases among cisgender women aged ≥15 years and pregnant persons during May 11–November 7, 2022. In addition, CDC identified all persons with mpox reported to CDC through national case surveillance and clinical consultations who were pregnant or recently pregnant regardless of gender identity. Detailed data regarding maternal and neonatal outcomes were obtained through enhanced pregnancy surveillance.§§ Statistical analyses were conducted using SAS statistical software (version 9.4; SAS Institute) and restricted to cases with available data. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.¶¶

37. Certain Reproductive Factors Play Causal Role in CVD for Women

Reproductive factors play a causal role in cardiovascular disease (CVD) in women, according to a study published online Feb. 27 in the *Journal of the American Heart Association*.

Maddalena Ardissino, M.B.B.S., from Imperial College London, and colleagues examined the causal role of reproductive factors on cardiovascular disease in

women using Mendelian randomization. Uncorrelated, genome-wide significant single-nucleotide polymorphisms were extracted from sex-specific genome-wide association studies.

The researchers found that earlier genetically predicted age at first birth increased the risk for coronary artery disease, heart failure, and stroke (odds ratios per year, 1.49, 1.27, and 1.25, respectively); partial mediators included body mass index, type 2 diabetes, blood pressure, and cholesterol traits. The risks for atrial fibrillation, heart failure, ischemic stroke, and stroke were increased with a higher genetically predicted number of live births (fewer than two versus two versus more than two: odds ratios, 2.91, 1.90, 1.86, and 2.07, respectively). Increased risks for coronary artery disease and heart failure were seen with earlier genetically predicted age at menarche (odds ratios per year, 1.10 and 1.12), with both associations partially mediated by body mass index.

"The findings support the emerging research focus on female-specific risk factors for CVD, by demonstrating that earlier first birth, higher number of live births, and earlier menarche are all associated with increased CVD in women," the authors write. "We stress the importance of routine evaluation of reproductive history in clinical risk stratification and consideration of targeted prevention strategies for women."

38. Sex Differences in the Prognostic Value of Troponin and D-Dimer Levels Among Patients With COVID-19

BACKGROUND

Male sex, elevated troponin levels, and elevated D-dimer levels are associated with more complicated COVID-19 illness and greater mortality; however, while there are known sex differences in the prognostic value of troponin and D-dimer in other disease states, it is unknown whether they exist in the setting of COVID-19.

OBJECTIVE

We assessed whether sex modified the relationship between troponin, D-dimer, and severe COVID-19 illness (defined as mechanical ventilation, ICU admission or transfer, discharge to hospice, or death).

METHODS

We conducted a retrospective cohort study of patients hospitalized with COVID-19 at a large, academic health system. We used multivariable regression to assess associations between sex, troponin, D-dimer, and severe COVID-19 illness, adjusting for demographic, clinical, and laboratory covariates. To test whether sex modified the relationship between severe COVID-19 illness and troponin or D-dimer, models with interaction terms were utilized.

RESULTS

Among 4,574 patients hospitalized with COVID-19, male sex was associated with higher levels of troponin and greater odds of severe COVID-19 illness, but lower levels of initial D-dimer when compared with female sex. While sex did not modify the relationship between troponin level and severe COVID-19 illness, peak D-dimer level was more strongly associated with severe COVID-19 illness in male patients compared to female patients (males: OR=2.91, 95%CI=2.63-2.34, p<0.001; females: OR=2.31, 95%CI=2.04-2.63, p<0.001; p-interaction=0.005).

CONCLUSION

Sex did not modify the association between troponin level and severe COVID-19 illness, but did modify the association between peak D-dimer and severe COVID-19 illness, suggesting greater prognostic value for D-dimer in males with COVID-19.

39. Anesthetic Care of the Pregnant Patient With CVD: Key Points

The following are key points to remember from an American Heart Association Scientific Statement on anesthetic care of the pregnant patient with cardiovascular disease (CVD):

1. **Maternal mortality rates** in the United States continue to exceed those of other well-resourced countries, with CVD cited as the leading cause. To address this shortfall, the authors emphasize the value of a multidisciplinary care team that includes obstetricians, cardiologists, maternal-fetal medicine physicians, anesthesiologists, intensivists, nurse specialists, and others, to provide comprehensive planning and care to pregnant patients with congenital or acquired CVD. During the peripartum period, the anesthesiologist assumes a key leadership role within the care team.

2. **Risk stratification tools,** including the maternal modified World Health Organization (mWHO) score, are helpful for triage decision-making, but important limitations of these tools exist. Maternal mWHO scores are derived from population-level data, and do not take into account quantitative features such as valve gradients that reflect individual patient risk. Class III conditions confer a significantly elevated risk of mortality, and Class IV conditions confer extremely high risk of maternal mortality. The peripartum care plan should be created early when possible, usually between 20-28 weeks, and documented clearly in the patient's medical record for transparent communication. The recommendation for Class III and IV patients is for delivery at a Maternal Level IV Care Center.
3. **Mode of delivery:** Shared decision-making on mode of delivery is important in all obstetrical patients, but even more so in patients with high risk of morbidity and mortality. **Vaginal delivery** is the preferred mode for most women with CVD, since it is associated with less blood loss, fewer wound infections, fewer thromboembolic events, and more gradual hemodynamic fluctuations. Assisted second stage should be considered in patients for whom prolonged Valsalva maneuver may pose risk of clinical deterioration due to fluctuation in preload (severe ventricular dysfunction, Fontan, or pulmonary arterial hypertension) or abrupt increase in sheer stress (high-risk aortopathy). **Cesarean delivery** may be appropriate when there is high risk of imminent maternal decompensation, or when expedited delivery facilitates coordination of postpartum interventions (including valvuloplasty or mechanical circulatory support). The anesthesiologist should advise the care team on the minimum time interval needed for interruption of anticoagulation that allows safe performance of neuraxial anesthesia, in accordance with American Society of Regional Anesthesia guidelines.
4. **Anesthesia for vaginal delivery:** Neuraxial labor analgesia decreases maternal plasma epinephrine and norepinephrine, lending support to epidural placement early in labor at the onset of painful contractions. A well-functioning epidural catheter provides a conduit for conversion to surgical anesthesia should emergency cesarean become necessary. The epidural catheter should be promptly replaced if it does not provide sufficient analgesia for labor. Use of saline rather than air for loss-of-resistance technique may decrease risk of venous air embolism in the event of intravascular needle placement. The risk-benefit of the traditional epidural test dose (lidocaine with epinephrine) should be considered carefully. Epidural medication should be titrated slowly over at least 10-

20 minutes to minimize risk of hypotension due to withdrawal of sympathetic tone.

5. **Anesthesia for cesarean delivery:** Neuraxial anesthesia is usually preferred versus general anesthesia, but indications for use of general anesthesia include cardiopulmonary decompensation necessitating tracheal intubation, maternal inability to tolerate supine positioning, concurrent anticoagulation, inadequate platelet count, or maternal refusal to undergo the neuraxial procedure.
6. **Monitoring and management:** Medications used during labor may have detrimental circulatory impact on the patient with CVD. Magnesium sulfate leads to hypotension, and terbutaline causes tachycardia and increased myocardial contractility. Sustaining adequate afterload is essential for maintaining coronary perfusion in patients with left ventricular (LV) hypertrophy, stenotic valvular lesions, LV outflow tract obstruction, or pulmonary hypertension. Decreased afterload may lead to hypoxemia in patients with intracardiac shunt, and prompt correction with vasopressors is critically important. Regurgitant valvular disease without significant stenosis may be associated with ventricular dilatation, and mandate avoidance of bradycardia or hypertension. Arterial pressure monitoring is standard in mWHO Class III-IV patients, and central venous pressure access and monitoring is mostly reserved for cases of cardiopulmonary decompensation including right ventricular (RV) failure requiring titration of vasopressors, inotropes, or pulmonary vasodilators, but may also be needed in patients with limited peripheral vascular access. Use of focused cardiac ultrasound to assess conditions including volume status, global LV and RV function, regional wall motion abnormalities, and pericardial effusion has been shown to reduce time to diagnosis and treatment.
7. **Prevention and management of postpartum hemorrhage (PPH):** Intravenous oxytocin infusion is a first-line uterotonic used for prevention of PPH. However, bolus administration or infusion rates exceeding the ED95 produce side effects including hypotension, without producing additional clinical benefit. Second-line uterotonic medications (carbaprost, methylergonovine) produce vascular and pulmonary side effects that may negatively impact patients with CVD, and are generally avoided. Use of obstetrical maneuvers including uterine compression sutures or Bakri balloon placement should be considered early. A large (>20,000 patient) randomized double-blinded trial of patients with PPH demonstrated that use of antifibrinolytic tranexamic acid within a 3-hour window reduced death attributable to bleeding without increased

incidence of thrombosis (excluding patients with coronary stent or cardiac arrest).

8. **Extracorporeal membrane oxygenation (ECMO)** may provide a last line of support for severe, refractory hypoxemia (venovenous ECMO) or ventricular failure (arteriovenous ECMO), and appears to improve survival if employed early during a clinical crisis. A cardiothoracic surgeon and perfusionist should be notified in advance if need for ECMO is anticipated.
9. **Recovery care:** Initiatives have been developed to help clinicians recognize signs of **undiagnosed or new-onset CVD.** Prompt evaluation is recommended for heart rate >120 bpm, SpO_2 ≤95%, respiratory rate >25, systolic blood pressure >160 mm Hg, or shortness-of-breath with minimal exertion. **Maternal cardiac arrest** occurs in 8.5/100,000 deliveries. Leading causes of arrest are hemorrhage (38.1%), heart failure or myocardial infarction (15.2%), amniotic fluid embolism (13.3%), and sepsis (11.2%). The anesthesiologist has multiple roles as code team leader. Resuscitation should be performed in a manner identical to that recommended by the AHA for adult patients (with the same compression ventilation ratios, use of backboard, airway support, medication, and defibrillation algorithms), with some added features. Key differences for the pregnant patient include left uterine displacement and preparation for fetal delivery concurrently with initial resuscitative efforts. Perimortem cesarean section should be performed within 4-5 minutes of cardiac arrest if the uterus extends up to or above the height of the umbilicus (~20 weeks of gestation).
10. **Future directions:** Optimal care of the obstetric patient with CVD remains poorly defined in many specific circumstances. There are numerous unanswered questions that would benefit from formal study. Multicenter registry data is cited as a potential source of information. Discussion of expanding anesthesia residency training to include greater emphasis on the disciple of cardio-obstetrics has been proposed by the authors.